Perioperative Fluid Management

Ehab Farag
Andrea Kurz
Christopher Troianos
Editors

Second Edition

Springer

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To the memory of my mom, Evangeline Troianos, and my father Achilles Troianos, to my wife Barb for her timeless love and unwavering support, and to my children and their spouses: Rachael, Andrew and Allison Troianos, and Rebecca Troianos and Justin Morris Christopher A. Troianos.

My sincerest thanks to my parents Mrs. Suzan Roufael and the late Mr. Samir Farag, to my wonderful wife Abeer, and to my dearest daughters Monica and Rebecca for their constant support, love, and encouragement.

Ehab Farag

Foreword

I have the honor of serving Cleveland Clinic alongside 66,000 caregivers. We share the vision to become the best place to receive care anywhere and the best place to work in healthcare. In the course of my work as a cardiac surgeon and CEO, I have the privilege of interacting with colleagues from a wide variety of backgrounds and professional interests.

Dr. Ehab Farag, Dr. Andrea Kurz, and Dr. Christopher Troianos with the Cleveland Clinic are the coeditors of *Perioperative Fluid Management*, *Second Edition*. Working with a renowned team of international contributors, they have developed a comprehensive study of perioperative fluid management. Their team is comprised of highly accomplished anesthesiologists, intensivists, and surgeons from the United States and Europe.

The team has explored perioperative fluid management in depth, ranging from the history of intravenous fluid to the recent and exciting opportunities to employ artificial intelligence. The book has clinical scenarios for almost every case in clinical practice. Their work is a testament to the importance of research, collaboration, and the need for continued innovation in healthcare. I believe their groundbreaking analysis will lead to improved patient care and foster further innovation.

I am pleased to recognize the importance of this work and to recommend *Perioperative Fluid Management*, *Second Edition*, to all the committed caregivers who work in the critically important field of fluid management.

Tomislav Mihaljevic
Cleveland Clinic
Cleveland, OH, USA

Preface for the Second Edition

Fluid management is still one of the most debated subjects in perioperative medicine. There are a lot of misconceptions and unsettled issues in perioperative fluid management. In the second edition of *Perioperative Fluid Management*, our motto is to present the most advanced evidence-based science in fluid management. Moreover, we tried our best not to leave a stone unturned in fluid management. In this edition, most of the chapters have been updated and revised from the first edition. The chapters on "Endothelial Glycocalyx and Revised Starling Principle" by Drs. Curry and Michel, the fathers of modern microcirculation, are of special recognition in this updated edition. We have added new chapters on the use of venous circulation in fluid management, the use of albumin in intensive care, and the use of dynamic arterial elastance in goal-directed fluid therapy. In addition, we have added new case scenarios in pediatric, obstetric, and intensive care patients to help clinicians have a strong armamentarium of fluid management strategies in every clinical scenario. We would like this edition, as was our intent for the previous edition, to be of benefit to all perioperative physicians in guiding fluid management.

Finally, we would like to express our gratitude to our colleagues who authored the book chapters and for their dedication to advancing the field. We would also like to thank the Springer publishing team for all their help and support during the publishing process of this book.

Editors

Cleveland, OH — Ehab Farag
Cleveland, OH — Andrea Kurz
Cleveland, OH — Christopher Troianos

Contents

Part I

Fundamentals of Fluid Management

A History of Fluid Management

1

Elizabeth A. M. Frost

Abstract

A history of fluid management is discussed focusing on the following key points: Bloodletting has been performed for more than 2000 years and is still used today, albeit for different reasons. While bloodletting was ordered by physicians, it was usually carried out by barber surgeons, thus dividing the two. Circulation of blood was not appreciated until William Harvey in the first century, and it was not immediately accepted as it was contrary to the teachings of Galen and others. The concept of the need for fluid replacement rather than bloodletting grew out of the worldwide cholera epidemic of the nineteenth century. Only over the past 60 years have fluids routinely been given intraoperatively.

Key Points

1. Bloodletting has been performed for more than 2000 years and is still used today, albeit for different reasons.
2. While bloodletting was ordered by physicians, it was usually carried out by barber surgeons, thus dividing the two.
3. Circulation of blood was not appreciated until William Harvey in the first century, and it was not immediately accepted as it was contrary to the teachings of Galen and others.
4. The concept of the need for fluid replacement rather than bloodletting grew out of the worldwide cholera epidemic of the nineteenth century.
5. Only over the past 60 years have fluids routinely been given intraoperatively.

The life of the flesh is the blood (*Leviticus* 17:11–14)
Take drink…this is my blood which is shed for you for the remission of sins (*Matthew* 26)

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Earliest Times

Long before biblical times, blood and body fluids were believed to have magical powers. Blood was the cornerstone of life and regarded as a gift. Hence, it was often used in sacrificial offerings to appease the gods. The Sumerians of Mesopotamia (4th–2nd millennium BCE) considered the vascular liver as the center of life [1, 2]. The priests of Babylon taught that there were two types of blood: bright red day blood in the arteries and dark night blood in the veins. In the *Yellow Emperor's Classic of Internal Medicine*, the *Nei Ching Su Wen*, an ancient Chinese text compiled about 4500 BCE, the heart and pulse were connected and all the blood was said to be under the control of the heart and flowed continually until death (Fig. 1.1) [3].

Egyptian physicians were aware of the existence of the pulse and also of a connection between the pulse and heart. The Smith Papyrus, ascribed by some to Imhotep who lived around 2650 BCE and was the chief official of the Pharaoh Dosier, offered some idea of a cardiac system, although perhaps not of blood circulation (Fig. 1.2) [4]. Distinction between blood vessels, tendons, and nerves was not

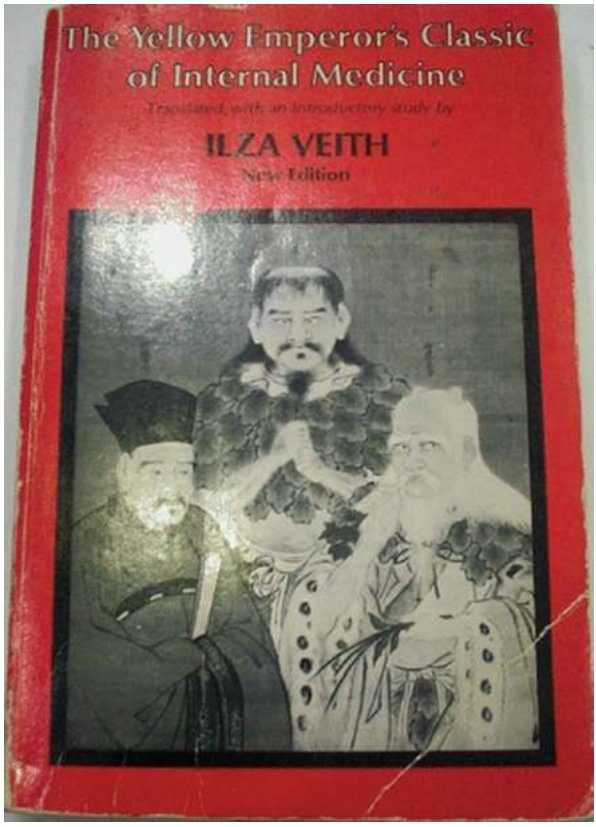

Fig. 1.1 The Yellow Emperor's classic of internal medicine. On page 34, one reads, "When people lie down to rest, the blood flows back to the liver"

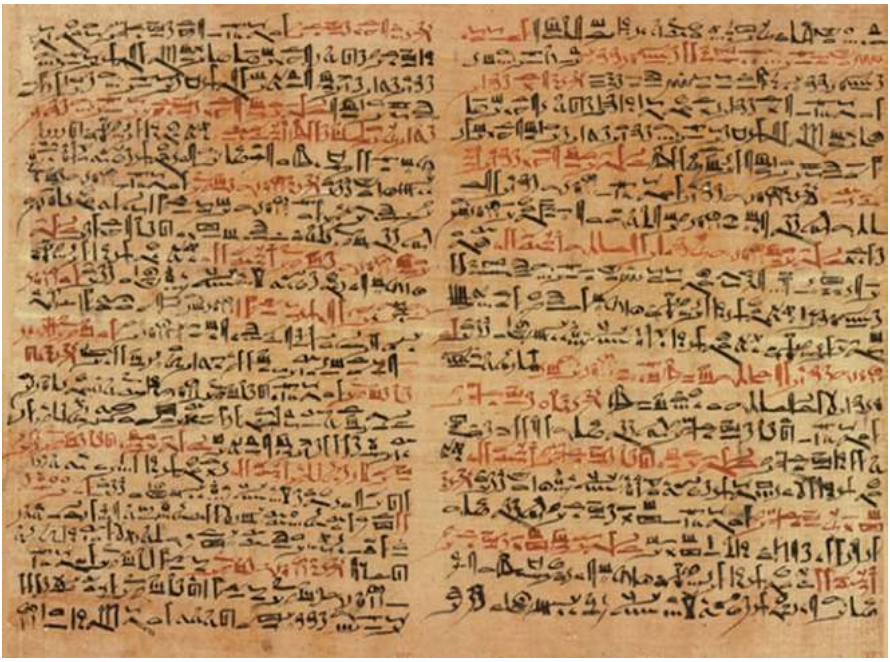

Fig. 1.2 The Edwin Smith Papyrus. The original is housed in the New York Academy of Medicine, NY, NY

made. A theory of "channels" that carried air, water, and blood to the body was analogous to the River Nile; if the river became blocked, crops were unhealthy. This principle was applied to the body: If a person was unwell, laxatives should be used to unblock the "channels."

Greek philosophers began investigations into the circulation also in the second millenium BCE. Aristotle, a physician of the fourth century BCE, believed that blood was manufactured in the heart and then distributed to other tissues [1]. Erasistratus, an anatomist of the third century BCE, is credited for his description of the valves of the heart. He also concluded that the heart was not the center of sensations, but instead functioned as a pump [5, 6]. He distinguished between veins and arteries but believed that the arteries were full of air and that they carried the "animal spirit" (*pneuma*). But Galen, in the second century CE, disagreed with Erasisratus, believing that blood was made in the liver and that it moved back and forth until it was consumed [7]. This theory remained unchallenged until 1628 when William Harvey published his treatise, *De Motu Cordis* [8].

Between the first and sixth centuries CE, consumption of the blood of Roman gladiators was said to cure epilepsy [9]. After the banning of gladiatorial fighting around 400 CE, it became the practice to drink the blood of executed prisoners, especially if they were beheaded. Epileptic patients were described as crowding around the scaffold, cups in hand, waiting to "quaff the red blood as it flows from

the still quavering body of a freshly executed criminal" [10]. There are some reports that this supposed cure for the "falling sickness" existed until the nineteenth century [9].

Consuming blood was also thought to restore youth. A fifteenth-century physician noted: "There is a common and ancient opinion that certain prophetic women who are popularly called 'screech-owls' suck the blood of infants as a means, insofar as they can, of growing young again. Why shouldn't our old people, namely those who have no [other] recourse, likewise suck the blood of a youth?—a youth, I say who is willing, healthy, happy and temperate, whose blood is of the best but perhaps too abundant. They will suck, therefore, like leeches, an ounce or two from a scarcely-opened vein of the left arm; they will immediately take an equal amount of sugar and wine; they will do this when hungry and thirsty and when the moon is waxing. If they have difficulty digesting raw blood, let it first be cooked together with sugar; or let it be mixed with sugar and moderately distilled over hot water and then drunk" [11].

Suggested as perhaps the first attempt at blood transfusion, three young boys were bled and the blood given to Pope Innocent VIII by his Jewish physician Giancomo di San Genesio in 1492 [1, 2]. It is, however, more likely that the pope drank the blood. Nevertheless, the boys and the pope all died and the physician disappeared. It is also possible that the story was circulated as an anti-Semitic campaign as the pope was very ill at the time.

Contrary to the idea of blood consumption was that propagated by the teachings of Charles Taze Russell, founder of the Bible Student Movement. He started publishing Zion's Watch Tower and Herald of Christ's Presence in 1879. In 1881 he founded Zion's Watch Tower Tract Society, later the Jehovah's Witness sect. Based on quotations from the Bible, members must abstain from eating blood, also interpreted as, receiving blood transfusions (Acts 15: 20,29, Genesis 9: 3–5, Deuteronomy 15: 14–23, Leviticus 7: 26, 27).

Bloodletting

Bloodletting derived from a belief that proper balance to maintain health was required between the four humors—blood, phlegm, black bile, and yellow bile—based in turn on the Greek philosophy of the elements of water, air, fire, and earth [12, 13]. Galen felt that blood was the dominant humor and the one most to be regulated. To balance the humors required removal of blood or purging. Aretaeus of Cappadocia, probably a first-century CE contemporary of Galen, advocated venesection for the treatment of "phrenetics": "If the delirium and fever have come on in the first or second day it will be proper to open a vein at the elbow, especially the middle" [14].

Bloodletting was the most frequently performed medical practice for more than 2000 years (Fig. 1.3) [15]. While trepanning of the skull allowed evil spirits to be released from the head, bloodletting facilitated the removal of the demons that caused disease from other parts of the body. The Egyptians used the

Fig. 1.3 Iatros, an ancient Greek word for "physician," is depicted on this old Grecian vase, bleeding a patient. The Peytel Arybalos, 480–470 BC, Louvre, Dpt.des Antiquites Grecques/Romaines, Paris. Photographer: Marie-Lan Nguyen, 2011 (Reprinted under Creative Commons license. https://creativecommons.org/licenses/by/3.0/deed.en)

technique at least by 1000 BCE, followed by the Greeks and Romans [12, 13]. While teaching that many diseases were caused by an overabundance in the blood, Erasistratus advocated initial treatment with vomiting, starvation, and exercise [6]. Overabundance or plethora was recognized by headache, tiredness, seizures, and fever. The practice of bleeding may have derived from the belief that menstruation occurred to "scourge women of bad humors" as taught by Hippocrates and Galen. Moreover, premenstrual cramps and pain were often relieved when blood flowed [1, 7, 16].

Precise instructions dictated how much blood should be removed based on age, general health, the season, and the weather. Either arterial or venous blood was drained depending on the disease. Blood vessels were identified depending on which organ they drained. The more severe the illness, the greater amount of blood was to be removed. Different religions laid down specific rules as to appropriate days; for example, select saints' days in the Christian calendar. Specific days of the week were also identified in the Talmud. The Talmud recommended specific days of the week and of the month for bloodletting [17]. Bleeding charts aligned bodily bleeding sites with the planets. Bloodletting was even used to treat hemorrhage before surgery and during childbirth to prevent inflammation. The amount of blood estimated to be in a limb was removed prior to amputation of that limb.

George Washington, the first US president, died on December 14th 1799 after having 3.75 l of blood removed from his body within a 10-h period as treatment for *cynanche trachealis* by Drs. James Craik and Gustavus Brown (most likely the president was suffering from a peritonsillar abscess, that would better have been managed by tracheostomy, as recommended by Dr. Elisha C. Dick who was overruled by the other two physicians because they were unfamiliar with the technique.) [18, 19].

Bloodletting was usually ordered by physicians but carried out by barber surgeons, thus dividing physicians from surgeons. The red-and-white-striped barber's

Fig. 1.4 Bloodletting woodcut from *Officia M.T.C* Cicero, 1531 (Source: Wellcome Library, London. Wellcome Images. Reproduced under Creative Commons Attribution 4.0 International license. https://creativecommons.org/licenses/by/4.0/)

pole represented gauzes wrapped around a stick [13]. The practice was standard treatment for all ailments, both prophylactically and therapeutically and persisted into the twenty-first century (Figs. 1.4 and 1.5) [13, 20].

Pierre Alexander Louis, a French physician of the nineteenth century, disagreed that fevers were the result of inflammation of the organs and bloodletting was an effective treatment for pneumonia [21, 22]. He published a paper in 1828 (expanded in 1834 to a book-length treatise in the *American Journal of Medical Sciences* entitled "An essay on clinical instruction"), demonstrating the uselessness of bloodletting. He met with strong resistance by physicians who refused to wait for reviews to determine if current treatments worked or change their practices of centuries. Gradually Louis' "numerical method" added objectivity to how patients should be treated to improve outcomes. He used averages of groups of patients with the same illness to determine effectiveness of therapies and accounted for age, diet, severity of illness, and treatments other than bloodletting. He also wrote of "averages" and "populations" and thus began the concept of "statistical probability."

During the early nineteenth century, leeches became popular (Fig. 1.6a, b). "Leech collectors," usually women, would wade into infested ponds, their legs bare. The leeches would attach themselves and suck several times their body weight of blood and then fall off, to be collected and sold to physicians [23]. In the 1830s, England imported about six million leeches annually for bloodletting purposes from France. Initially a very inexpensive treatment, scarcity of the little worms drove the price up and the treatment became less popular [23].

Fig. 1.5 An old photo of bloodletting during the nineteenth century. From the collection of the Burns Archive, PD-US

Fig. 1.6 (**a**) An artistic representation of a woman who is self-treating with leeches from a jar (Source: van den Bossche G. *Historia medica, in qua libris IV. animalium natura, et eorum medica utilitas esacte & luculenter.* Brussels: Joannis Mommarti, 1639. US National Library of Medicine). (**b**) Leeches as they were purchased in a jar

Beginnings of Intravenous Therapy

In 1242, an Arabian physician, Ibn al Nafis, accurately described the circulation of the blood in man [24]. He wrote: "The blood from the right chamber of the heart must arrive at the left chamber but there is no direct pathway between them. The thick septum of the heart is not perforated and does not have visible pores or invisible pores as Galen thought. The blood from the right chamber must flow through the vena arteriosa to the lungs, spread its substances, be mingled there with air, pass through the arteria venosa to reach the left chamber of the heart and there form the vital spirit…" [24].

Nevertheless, credit for the discovery of the circulation is generally given to William Harvey. He concluded: "The blood is driven into a round by a circular motion and that it moves perpetually and hence does arise the action and function of the heart, which by pulsation it performs" [8].

Harvey first presented his thesis, *De Motu Cordis*, at the Lumleian lecture (a series started in 1582) of the Royal College of Physicians in 1616 [25]. His insights evolved over several years thereafter and were finally published in 1628 in Latin in a 72-page book in Frankfurt, probably because that venue was host to an annual book fair that would allow the work greater attention [8]. The treatise was not translated into English until 1653. Such views of the circulation were contrary to the teachings of Galen and thus Harvey's work was not immediately appreciated. Indeed, his practice suffered considerably, but no doubt the dedication of the book to King Charles I, to whom he was personal physician, helped in the ultimate acceptance of his conclusions and set the stage for intravenous therapy and fluid administration. Harvey did not know of the capillary system, the discovery of which is later ascribed to Marcello Malpighi, but he did describe fetal circulation [24].

Andreas Libavius, a German alchemist, imagined how blood could be taken from the artery of a young man and infused into the artery of an old man to give the latter vitality. Although he described the technique quite accurately in 1615, there is no evidence that he actually transfused anyone [1, 24]. The same can be said for the Italian, Giovanni Colle da Belluno, who mentioned transfusion in 1628 in his writings on "methods of prolonging life" [24].

Perhaps the first person to conceive of transfusion on a practical basis was the Vicar of Kilmington, in England, the Rev. Francis Potter [26]. Described as a reclusive eccentric, he was befriended by John Aubery, a close acquaintance of Harvey. Aubery an English antiquary and writer, recorded of Potter in 1649: "He then told me his notion of curing diseases by transfusion of bloud out of one man into another, and that the hint came into his head reflecting on Ovid's story of Medea and Jason, and that this was a matter of ten years before that time" [27].

Potter used quills and tubes and attempted transfusion between chickens but with little success.

Francesco Folli, a Tuscan physician, claimed to be the originator of blood transfusion [28]. He was aware of Harvey's work and felt it possible to cure all diseases and make the old young by transfusing blood. At the Court of the Medici he had given a "demonstration" of transfusion (it actually may only have been by diagrams)

to Ferdinand II, Duke of Tuscany, who was not impressed and dismissed Folli. The latter went into seclusion and was unaware of the several advances by Richard Lower, Jean Baptists Denys, and others in the intervening years before he rushed to print a book, *Stadera Medica* (the Medical Steelyard, Florence, GF Cecchi, 1680), in which in a second section "Della Trasfusione del sangue" he asserted his claim as the inventor. He weighed the pros and cons of blood transfusion writing: "Discovered by Francesco Folli and now described and dedicated to His Serene Highness, Prince Francesco Maria of Tuscany." He postulated that 20 young men as donors could allow the patient to get fresh blood over a considerable time. He described his apparatus as a funnel connected by a tube from a goat's artery with a gold or silver cannula in the patient's arm [24]. Later he recanted and noted that it would be impertinent of him to give directions about an operation that he himself had never attempted [28].

Richard Lower, a Cornish physician, is credited as the first to perform a blood transfusion between animals (xenotransfusion) and from animals to man [29, 30]. Working with Christopher Wren, he performed a successful transfusion in 1665 by joining the artery of one dog to the vein of another by means of a hollow quill. Lower's major work, *Tractatus de Corde*, was published in 1669 and traced the circulation through the lungs, differentiating between arterial and venous blood. Believing that patients could be helped by infusion of fresh blood or removal of old blood, Lower transfused blood from a lamb to a mentally ill man, Arthur Coga, before the Royal Society on November 23, 1667. The procedure was recorded in Samuel Pepys' diary:

> …with Creed to a tavern and a good discourse among the rest of a man that is a little frantic that the College had hired for 20 shillings to have some blood of a sheep let into his body…I was pleased to see the person who had had his blood taken out…he finds himself better since but he is cracked a little in his head [2].

The same year, a French physician, Jean Baptists Denys, had administered the first fully documented human blood transfusion on June 15, 1667 [31, 32]. Using sheep blood, he transfused about half a pint into a 15-year-old boy, who had been bled with leeches 20 times (Fig. 1.7). Surprisingly, the boy recovered. Denys' second attempt at transfusion was also successful. However, his third patient, Baron Gustaf Bonde, died. Later in 1667, undeterred, Denys transfused calf's blood to Antoine Mauroy, who also died. Denys was accused by Mauroy's wife of murder. He was acquitted, and it was later found that the patient had died of arsenic poisoning. But considerable controversy arose and in 1670 blood transfusions were banned until the first part of the nineteenth century (around 1818) when James Blundell, using only human blood, saved a number of postpartum women who had almost bled out. He wrote: "appalled at my own helplessness at combating fatal hemorrhage during delivery" [2].

Blundell experimented by exsanguinating dogs and then reviving them by transfusing arterial blood from other dogs. He concluded that blood replacement had to be species-specific using initially vein-to-vein transfusion (Fig. 1.8). He later introduced the use of the syringe, noting that air must be removed and the problem of clotting: "…the blood is satisfactory only if it allowed to remain in the container for but a few seconds" [24].

Fig. 1.7 Early transfusions were carried out between animals and humans. In this early illustration, blood is transfused from a lamb into a man. Wellcome Library, London (Reprinted under Creative Commons Attribution only license CC BY 4.0)

Fig. 1.8 Illustration of Blundell's human-to-human blood transfusion (Source: Blundell J. Observations on transfusion of blood. *Lancet*. Saturday, June 13, 1828; vol. II)

Only with the discovery of the four groups of blood by Karl Landsteiner in 1900 did transfusion become safer and popular again.

(Of note, perhaps, is as recently as 60 years ago, the author of this chapter transfused blood from a young man to a woman during a cesarean section for umbilical prolapse at a small hospital in the mountains of Switzerland. The hospital maintained documentation of the blood type of all the inhabitants of the village. When blood was needed, the type was determined and the appropriate villager instructed to come to the hospital. Basic compatibility was then established and blood drawn in 20 ml aliquots and immediately infused to the patient).

Intravenous Infusions of Drugs and Fluids: Mainly in Dogs

Sir Christopher Wren, along with Robert Boyle, experimented extensively with intravenous administrations of many substances in animals [33]. An animal bladder attached to two quills was designed to infuse beer, wine, opium, and other drugs. A large dog was selected. Venous access was achieved and the vein stabilized with a brass plate. As reported in one of the initial experiments, opium and alcohol were injected (tincture of opium, which had long been used orally) resulting in a brief period of anesthesia. The dog on trying to get up immediately became disoriented. After a period during which the dog was kept moving to assist recovery, a full recovery was made. Thomas Sprat in a history of the Royal Society recorded in 1657: "Wren was the first author of the Noble Anatomical Experiment of Injecting Liquors into the Veins of animals: an experiment now vulgarly known but long since exhibited to the Meetings at Oxford, and thence carried by some Germans and published abroad. By his operation, Creatures were immediately purged, vomited, intoxicated, killed or revived according to the quantity of Liquor injected" [24].

Wren himself described the initial experiments carried out in Boyle's quarters on High Street in Oxford in 1656 in a letter to a friend, William Perry in Ireland: "I have injected Wine and Ale in a living Dog into the Mass of Blood by a Veine, in good quantities till I have made him extremely drunk but soon after he Pisseth it out" [33–36].

It is surprising that given the apparent anesthetic state realized in the dogs that a potential for intravenous anesthesia during surgery in humans was not realized. Difficulty in gaining and maintaining intravenous access, the political climate, wariness regarding the technique, and observations that the amount of drug that would be effective was impossible to judge may all have been factors. It is also possible that the players were more interested in other pursuits—Wren as an architect, Boyle as a chemist, Willis in anatomy of the central nervous system, Robert Hooke as philosopher and machinist [35]. Or these experiments may have been viewed as merely a diversion from the real work of the day.

Early Attempts with Needles and Syringes

Until the beginning of the nineteenth century, infusion of blood and other substances was by direct cannulation of vessels using a quill or some other tube. Basically, a

syringe is a simple pump and it is likely that syringe-type devices were produced by many people. The earliest and most common syringe-type device was called a "clyster"—a device for giving enemas. There were numerous parallel processes of evolution and experimentation that led to the development of the hypodermic syringe devices to inject drugs and medicines. Thus, several people have been credited with the "invention" of the syringe. In 1807, the Edinburgh Medical and Surgical Dictionary defined a syringe as: "A well-known instrument, serving to imbibe or suck in a quantity of fluid and afterwards expel the same with violence. A syringe is used for transmitting injections into cavities or canals" [37].

Mr. Fergusson, of Giltspur Street in London, devised a glass syringe, used in 1853 by Alexander Wood for the subcutaneous injection of opiates for the relief of pain [38]. Wood improved on the design, attaching a hollow needle that had been invented by Francis Rynd in Ireland and attaching it to a syringe. He published a description of the subcutaneous injection of fluid drugs for therapeutic purposes in 1855 [39, 40]. Wood believed that the action of opiates administered by subcutaneous injection was mainly localized. Using a syringe, he thought, would allow greater accuracy in administering the drug in close proximity to a nerve, providing better pain relief. Around the same time, Charles Pravaz of Lyon also experimented with subdermal injections in sheep using a silver syringe measuring 3 cm (1.18 in) long and 5 mm (0.2 in) in diameter. Pravas's syringe had a piston that was driven by a screw so he could administer exact dosages. The glass of Wood's syringe allowed for more accurate dosing [36].

Wood also believed that by injecting morphine into the arm, the problem of addiction could be solved [41]. Given orally, morphine increased the appetite but that was not the case if given intravenously [41]. Although it was reported that Wood's wife died of intravenous morphine at his hand, that is probably not true as she outlived him by 10 years, dying in 1894 [41]. During the American Civil War (1861–1865), an estimated 400,000 soldiers became addicted to morphine, a number that may be underestimated as as addiction was not recognized as a medical condition and veterans were at risk of losing their job if it became known that they depended on drugs Given that surgery was traumatic without anesthesia, the use of morphine began to spread. Opium pills were widely dispensed when hypodermic needles were unavailable. During the Civil War, solders were often dosed with enormous amounts of morphine or opium to kill pain. While the potential for addiction was already known, simple humanitarian concerns ensured that soldiers remained liberally dosed with morphine.

Anecdotal accounts of Civil War doctors on both sides dispensing opium are common. One Confederate doctor, William H. Taylor, gave a plug of opium to every patient reporting pain. A Union doctor, Nathan Mayer, diagnosed patients from horseback. If the wounded soldier needed morphine, Mayer would pour out an "exact quantity into his hand and have him lick it off. "Soldiers' Disease" was ascribed to the returning veteran: "…Identified because he had a leather thong around his neck and a leather bag with morphine sulfate tablets, along with a syringe and a needle issued to the soldier on his discharge" [41].

As Kane noted in his book, *The Hypodermic Injection of Morphine*: "There is no proceeding in medicine that has become so rapidly popular; no method of allaying pain so prompt in its action and permanent in its effect; no plan of medication that has been so carelessly used and thoroughly abused; and no therapeutic discovery that has been so great a blessing and so great a curse to mankind than the hypodermic injection of morphia" [42].

The Cholera Epidemic

Clouds have a silver lining could not be more true than what black, thick, cold blood in collapsed and dead patients led physicians to believe that the cure lay in bloodletting, inducing vomiting, and dosing with calomel, this last remedy used as a means of "unlocking the secretions" [43]. By the end of 1832, there were at least 23,000 cases in England with a mortality rate of 33% [43, 44]. The first death in England had occurred in Sunderland on October 26, 1831. There appeared to be a high incidence of cholera in that part of the country, a finding that attracted the attention of a 22-year-old recent medical graduate from the University of Edinburgh, William O'Shaughnessy. He read a paper before the Westminster Medical Society on December 3, 1831, which was later published in the *Lancet*, pointing out the high mortality rate of cholera and asking if: "the habit of practical chemistry which I have occasionally pursued…might lead to the application of chemistry to its cure… (and describing the end result of the disease as)… the universal stagnation of the venous system and the rapid cessation of the arterialization of the blood are the earliest as well as the characteristic effects…hence the skin becomes blue… if…we could bring certain salts of highly oxygenated constitution fairly into contact with the black blood of cholera, we would certainly restore its arterial (oxygenated) properties and most probably terminate the bad symptoms of the case" [45].

Shortly after his address, O'Shaughnessy went to Sunderland to learn more about the disease and the therapies used [46]. He carried out analyses on the blood and excreta of several victims and concluded that the blood "has lost a large proportion of its water…it has lost also a great proportion of its and neutral saline ingredients" [47, 48].

As the disease spread to London, O'Shaughnessy made a further report to the Central Board of Health with "therapeutic conclusions": "the indications of cure…are two in number—viz. first to restore the blood to its natural specific gravity; second to restore its deficient saline matters…the first of these can only be effected by absorption, by imbibition, or by the injection of aqueous fluid into the veins. The same remarks, with sufficiently obvious modifications apply to the second…When absorption is entirely suspended…in those desperate cases…the author recommends the injection into the veins of tepid water holding a solution of the normal salts of the blood" [43].

Although O'Shaughnessy completed detailed analyses of the bodily fluids of many cholera victims, and even experimented with intravenous infusions in

animals, he did not extend his treatment to humans, although his descriptions are precise: “When the current of the circulation is impeded, as in the blue cholera, injections from the bend of the elbow can scarcely be efficient. I would, therefore, suggest that the tube, which should be of gold or silver, be introduced into the external jugular vein immediately as it crosses the sternomastoid muscle. The syringes should contain no more than 3 ozs, the solvent should be distilled water heated to a blood warmth and the syringe also equally warmed. The tube should not be more than an inch long and curved gently for the convenience of manipulation and it should have a marked conical form. After the vein is exposed, I would make a puncture with a lancet just sufficient to permit the introduction of the tube. Injection should be deliberately and slowly performed” [49].

While O’Shaughnessy understood the need to replace electrolytes, at about the same time, others had recognized the need for fluid replacement and injected water. Jaehnichen and Hermann, both from the Institute of Artificial Waters in Moscow, during the same cholera epidemic may have injected 6 oz. of water into a cholera patient who appeared to rally briefly but died 2 h later [50, 51]. However, based on a report made later by Jaehnichen, it is doubtful that venous injections were made, rather suggestions were offered [52]. Others also injected water intravenously and a few attempts were made with hypertonic saline but without success [53].

A few weeks after O’Shaughnessy’s publications in the *Lancet*, Thomas Latta, a general practitioner in Leith, adopted the former’s principles. He did not seek publicity or claim originality [44]. He noted that he “attempted to restore the blood to its natural state, by injecting copiously into the larger intestine warm water, holding in its solution the requisite salts and also administered quantities from time to time by the mouth” [44, 49].

Finding that this approach provided no benefit, and indeed sometimes only increased the vomiting and diarrhea, he “at length resolved to throw the fluid immediately into the circulation” [54].

He described his first case, an elderly, moribund woman, who at the start of treatment was pulseless. He inserted a tube into the basilic vein and cautiously began to infuse 6 pints of salt solutions. The patient responded and appeared to have recovered completely. Latta left her with the general surgeon. Unfortunately, a short period later, the vomiting returned and she relapsed and died. Latta wrote: “I have no doubt the case would have issued in complete reaction had the remedy which already had produced such effect been repeated” [54].

Three weeks later, on June 16, 1832, Latta detailed three further cases in a letter to the editor of the *Lancet* [55]. The intravenous infusion consisted of muriate of soda and subcarbonate of soda in 6 pints of water, calculated at 58 meq/l sodium, 49 meq/l chloride, 9 meq/l bicarbonate [44]. The solution was strained through chamois leather. Initially, Latta warmed the solution but later felt it preferable to place the patient in a warm bath. He also increased the saline matter by one third [56, 57]. He recognized that repeated infusions were necessary and in one case he gave 330 oz. over 12 h (about 10 l). The therapy was not immediately accepted, as of the first 25 reported cases, only eight recovered—probably because treatment was delayed until the patients were practically moribund and infusions were not

continued after the initial attempts [43]. However, Latta did have one important supporter, Dr. Lewins, a colleague who encouraged him to report his findings to the Central Board of Health. Lewins described the work as "a method of medical treatment which will, I predict, lead to important changes and improvements in the practice of medicine" [58].

In his communication to the Central Board, Latta described how he injected the solution, using Reid's patent syringe. He emphasized the need to avoid accidental introduction of air into the veins [59]. Despite the fact that 12 out of 15 patients treated with intravenous solutions had died, the Board considered this was a favorable result and praised Latta for his scientific zeal [60].

John Mackintosh, a prominent Edinburgh physician was an early supporter of Latta, although he too advocated saline infusion as a last measure [53]. He described the method of infusion that was to be injected at 106–120 °F. Solid particles of saline could be strained through leather rather than linen. Reed's syringe was a large, two-way device with ball valves, connected by a tube that often corroded. Two persons were required for the procedure and up to 5 l could be injected in 30 min [53]. Mackintosh noted that rigors almost invariably followed the infusions, commencing, sometimes, during the infusions. He suggested that the fluid should be made as close as possible to serum and added albumen from eggs to the solution, without apparent improvement. Mackintosh felt that as the survival from cholera was only 1:20 in severe cases and 1:6 with saline infusions, the latter therapy was beneficial [53]. Sugar, cod liver oil, milk, and honey were all suggested as additives, but few other advances were made [61].

Improving the Infused Solution

The cholera epidemic died down in Britain and physicians became less intent on replacing fluids intravenously. The main protagonists of the practice were no longer around. Latta died in 1833 and O'Shaughnessy went to India where he became involved in developing telegraphic communications and also later introduced the therapeutic use of *Cannabis sativa* to Western medicine for the treatment of tetanus, epilepsy, and rheumatism [62].

But cholera continued in the Americas. Nevertheless, the use of intravenous saline was not generally accepted. It was often given only to those who were about to die and the public felt that the therapy hastened death. Also, not understanding that severely dehydrated patients can no longer lose fluids, it was felt that rehydration would provoke further purging. Treatment was rarely continued as Latta had suggested. Perhaps also and of equal importance, the fluid was not sterile, chemically impure, and very hypotonic. Thus, the more fluid that was infused, the greater the risk of bacteremia, fever, and hemolysis [43]. Many patients who might have recovered from cholera either died quickly of air embolism or slowly from sepsis [50].

Gradually, over the next 100 years principles of asepsis and anesthesia developed. The notion that disease could be transferred by very small particles was raised by an Italian physician, Girolamo Fracastoro, in the sixteenth century. He authored

a book in which he expounded on his theories, but they were not widely accepted [63]. He used the Latin word *fomes* in 1546, which means tinder, implying that books, clothing, etc., can harbor and hence spread disease. From this word comes "fomites."

Some 200 years later, and shortly before Louis Pasteur's work, Agostino Bassi, an Italian entomologist, introduced the idea of microorganism as a source of disease [64]. Pasteur, working in Paris in the second half of the nineteenth century, developed the concept that without contamination, microorganisms cannot grow [65, 66]. Using sterilized and sealed flasks he demonstrated that nothing developed until the flasks were opened. Joseph Lister, professor of surgery at the University of Glasgow, furthered the idea of antisepsis and the germ theory of disease, noting especially the importance of clean wounds in surgery to allow healing [67]. At that time, a mark of a good surgeon was the amount of dried blood he had on his coat, often a black frock coat. Lister used carbolic sprays in his operating theaters at the Glasgow Royal Infirmary (Fig. 1.9). He also noted that the infection rate in the wards of the hospital that abutted the necropolis was greater than at the other end—perhaps due to the decomposing bodies that awaited burial outside the windows on the cemetery side. Over three papers to the *British Medical Journal* and the *Lancet*, he laid out the necessity for germ control [67–69].

Concurrently, other advances in the understanding of intravenous solutions were made. Jean-Antoine Nollet first documented observation of osmosis in 1748 [70] and Jacobus Henricus van't Hoff, a Dutch physical chemist, was awarded the Nobel Prize for Chemistry in 1901, for work on rates of chemical reaction, chemical equilibrium, and osmotic pressure [71].

Attention again returned to infused solutions. A few studies were carried out in 1882–1883 by a Dutch physiologist, Hartog Jacob Hamburger, on concentrations of salt solutions. He deduced, based on looking at red cell lysis, that 0.9% was the concentration of salt in human blood. In 1896, he described the crystalloid solution known as Hamburger's solution or normal saline. Based on plant-based experiments by a botanist, Hugo de Vries, Hamburger developed a salt solution that was thought

Fig. 1.9 Lord Joseph Lister's carbolic spray in the Hunterian Museum at the University of Glasgow

to have the same osmolality as human blood and therefore could not hemolyze red blood cells. Whether saline was ever originally intended for intravenous administration is not known [72]. Matas in the United States published a case report of the use of an IV infusion of saline for the treatment of shock in humans [73]. Some years later, he described a continuous "drip" technique using glucose [74].

The next major advance came from a British cardiovascular physiologist, Sidney Ringer, who was attempting to study isolated hearts, also during the 1880s, to determine what might keep them beating normally [75]. He used a saline solution consisting primarily of sodium, potassium, and chloride ions, with an added buffer using distilled water to prepare his solutions. However, he found that the isolated heart muscle soon failed to contract. A somewhat anecdotal story reports that one day cardiac action continued for hours [76, 77]. Apparently, having run out of distilled water, a lab technician had used river water, which contains many minerals including calcium. This accidental discovery led to the finding that heart muscle, unlike skeletal muscle, requires extracellular calcium to contract.

During the 1930s, Ringer's solution was further modified by an American pediatrician, Alexis Hartmann, for the purpose of treating acidosis. He added lactate to attenuate changes in the pH by acting as a buffer for acid. Thus, the solution became known as "Ringers lactate solution" or "Hartmann's solution" [78].

Another important development came with the realization that despite sterilization, febrile reactions were still common. Seibert discovered in 1923 that sterilized and stored metabolic by-products of microorganisms, pyrogens, were formed if distilled water was not used [79].

Needles and Syringes

Now that sterilization and osmolarity were better understood, means to infuse fluids more conveniently and safely became important.

As noted earlier, Wood can be largely credited with the popularization and acceptance of injection as a medical technique, as well as the widespread use and acceptance of the hypodermic needle [39, 40]. But the basic technology of the hypodermic needle stayed largely unchanged as medical and chemical knowledge improved. Small refinements were made to increase safety and efficacy, with needles designed and tailored for particular uses after the discovery of insulin. Banting, a Canadian surgeon had persuaded John Macleod in Toronto to lend him some lab space. During the latter's absence and working with his assistant Charles Best, they were able to identify insulin (named after the Islets of Langerhans) in 1921 [80]. Insulin was to be given intravenously.

During the early part of the twentieth century, "IV feedings" were only given to the most critically ill patients. Fluids, usually boiled, were poured into an open flask, which was covered with gauze. A rubber stopper attached to either glass or rubber tubing was inserted into the neck. An extra needle was pushed through the stopper for venting purposes. The bottles were all reused as was the tubing. A metal screw clamp allowed for flow adjustment. A nurse stayed with the patient during the

infusion [81]. Hospital pharmacies usually made their own solutions. Cleansing the skin with alcohol prior to needle insertion was not common practice. Needles were large, usually 14–16 g, and also reusable (Fig. 1.10a–e). Most were made of steel. A stylet kept the lumen open. Small, 1-in., 22 gauge scalp vein needles for babies were also available. There were three main methods of intravenous administration of drugs: a new venipuncture each time, a continuous infusion through a hypodermic needle, and venous cut-down. This last technique, usually performed at the ankle, required tying off of the vein, prior to its opening and threading in a small plastic catheter. Prior to the advent of autoclaving in the 1950s, all materials were sterilized with boiling water. Even gauzes, usually handmade, were sterilized in metal canisters and accessed using sterile forceps.

Fig. 1.10 (**a**–**e**) An assortment of early needles and syringes

Anesthesia was also advancing from the early days of inhalation agents. In 1869, Oskar Liebreich advocated chloral hydrate as an induction agent [82], a technique put into practice briefly by Pierre-Cyprien Ore in 1872 [83]. However, the high mortality rate discouraged use of this drug. David Bardet used "Somnifen" in 1921 [84]. This barbiturate derivative had a low solubility and long duration of action but was also not well received. However, the idea of an induction agent was considered of considerable value to allay the fears of patients before entering the operating room. "Pernosten" was introduced in 1927, and in 1932 [85], Weese and Scharpff synthesized hexobarbital [86].

Volwiler and Tabern, working for Abbott Laboratories, discovered pentothal in the early 1930s [87]. Ralph Waters in Wisconsin first used it in humans in March 1934. He found the drug to have short-lived effects and little analgesia. Some 3 months later, John Lundy at the Mayo Clinic started a clinical trial of thiopental [88]. Although reported at the time, thiopenthal probably was not responsible for large numbers of deaths at Pearl Harbor. A more recent report suggests gross exaggeration: Out of 344 wounded that were admitted to the Tripler Army Hospital only 13 did not survive, and it is not likely that thiopental overdose was responsible for more than a few of these [89].

Although induction doses of IV anesthetics became the norm, fluid infusions were not necessarily added. Certainly through the 1960s in Great Britain, it was standard practice to secure a vein with a right-angle steel needle. A moveable arm with a rubber patch on the outside of the skin was then moved to cover the hole of the needle within the vein. Should fluid or blood be required, small amounts could be injected via syringe or by presterilized and packaged infusion set. These sets did not have filters when blood was given (personal recollection, Glasgow Royal Infirmary 1963).

During World War II, partially disposable syringes were developed for administration of morphine and penicillin in the battlefield. Working independently during the 1940s, Meyers and Zimmerman devised through the needle cannulation with a flexible tube to allow indwelling catheters that afforded greater mobility to patients over rigid needles [90, 91]. Thrombosis within the catheter was decreased by the addition of silicone. Massa, Luny, Faulconer, and Ridley introduced an apparatus in 1950 consisting of a metal needle stylet, a cannula hub, and an indwelling plastic cannula that was the forerunner of the catheter around the needle design [92, 93]. It became known as the Rochester needle, to be sold in unsterile packages of 12 (Fig. 1.11) [94]. Lundy later refined the design to a two-piece plastic catheter over a plastic stylet in 1958 [95]. The same year, an anesthesiologist from Colorado, George Doherty, came up with the scheme for the intracath: a plastic catheter through a steel needle [96].

Plastics were also becoming more commonly used [97, 98]. Baxter Travenol, a major manufacturer of intravenous equipment, was founded in 1931. The first IV solutions were marketed by that company in vacuum bottles by 1933 [61]. But the complications of IV infusions remained high, such that one physician predicted that "this is a passing new-fangled notion" [61].

Fig. 1.11 A nonsterile package of 12 small, reusable needles

He referred to problems such as "speed shock" that caused systemic reactions when the fluid was run in too fast [61]. There were no injection sites and no way to remove air. Fatal air embolism resulted when blood was administered under pressure by pumping air into the bottle to increase the rate of infusion. As soon as the bottle emptied, air was forced into the circulation. Glass bottles were at risk of falling off unstable stands and landing on patient's heads. Plastic IV tubing replaced rubber tubing beginning in the 1950s and plastic bags were introduced in the 1970s. The risk of air embolism diminished with the introduction of vented bottles. But still there was little training for physicians and nurses in fluid administration [81].

That IV infusion was not a fad was borne out by the end of World War II when Baxter had supplied the US military with more than four million bottles.

With the rise of awareness of cross-contamination from used needles, the need for a fully disposable system was realized. A New Zealand pharmacist, Colin Murdoch, met this challenge in 1956. His design was said to be "too futuristic" by the New Zealand Department of Health and he was advised that it would not be received well by doctors and patients. Murdoch worked on many permutations of his device for drug injection, vaccination, infusions, and as tranquilizer darts. Development of his invention was held off for several years due to lack of funding. Eventually, he was granted the patent and the syringe became a huge success [99].

Infusion Rates

Considerable controversy arose over how much and when to infuse fluids.

After observing and treating wounded soldiers during World War I, W. B. Cannon, an American physiologist, concluded that IV fluid infusion before surgical control

would have the deleterious effect of actually promoting hemorrhage. He concluded: "hemorrhage in the case of shock may not have occurred to a marked degree because blood pressure has been too low and flow too scant to overcome the obstacle offered by a clot. If the pressure is raised before the surgeon is ready to check any bleeding that may take place, blood that is sorely needed may be lost" [100, 101].

Cannon was later appointed professor and chairman of the Department of Physiology at Harvard Medical School. He coined the term "fight-or-flight response" and expanded on Claude Bernard's concept of homeostasis. Several years later, Wangensteen repeated this concern for early and aggressive fluid replacement when he reported that large volumes of IV crystalloid might be harmful in a patient with a source of bleeding, not readily accessible to pressure [102]. Despite the fact that several experimental data substantiated these conclusions, standard teaching remained that all hypotensive patients with suspected hemorrhage should receive fluids prior to surgery in an attempt to elevate blood pressure to so-called normal levels. This "science" derived from animal experiments in which blood was removed by withdrawal through a catheter, atraumatically to a predetermined endpoint of pressure or volume over a set time period [103]. The Wigger's model, for example, bled dogs down to a set blood pressure, which was maintained for 2–4 h [104]. A state of irreversible shock could be achieved in the lab. A few years later, Shires and Dillon, using a similar preparation, showed that the addition of large volumes of fluids to the reinfused blood enhanced survival over that achieved with blood replacement alone [105, 106]. Convinced of the error of striving for an increased blood pressure in traumatic hypovolemic shock in patients with vascular injury, Bickell conducted a prospective clinical trial evaluating the timing of fluid resuscitation for hypotensive patients with torso injuries [107]. Delaying fluids until the time of operative intervention improved survival and decreased the length of hospital stay. Pointing out that the trauma population is not a homogeneous group, but rather one with enormous physiologic complexities, depending not only on associated injuries, the degree of blood loss, age, the ability to compensate, and comorbidities, Bickell noted that treatment recommendations must be modified from a "one size fits all" Scheme [108].

Shires turned his attention to fluid replacement during elective surgical procedures. He noted that during the perioperative period, there are acute changes in renal function. He conducted a study with two groups of patients: The control group consisted of five patients undergoing minor surgery with general anesthesia (cyclopropane and ether) and the second group (13 patients) underwent elective major surgical procedures (cholecystectomy, gastrectomy, and colectomy) [109]. Plasma volume, red blood cell mass, and extracellular fluid volumes were measured in all patients on two occasions during the operative period by using I^{131} tagged serum albumin, chromate^{51} red blood cells, and sulfur^{35} tagged sodium sulfate. Shires determined that the loss of functional extracellular fluid was due to an internal redistribution due to surgery; in other words, there is a "third space" that must be replaced [109]. His findings were confirmed in the exsanguinated dog model described earlier, which did better with immediate fluid rather than blood replacement [105].

These conclusions were argued by Moore (a surgeon from Boston), who postulated that a metabolic response to surgical stress caused sodium and water retention and perioperative fluid restriction was indicated [110]. The debate prompted a combined editorial by Shires and Moore, both of whom urged moderation [111].

Nevertheless, the excessive fluid doctrine to replace the "third space" won. An article had appeared in 1957 from Holliday and Segar [112]. They concluded that the systems currently in place to guide fluid replacement using complex formulae and nomograms in general were inefficient and would not gain widespread acceptance. Thus, they suggested a 100–50–20 rule as a base guideline, essentially for children on a daily basis. They compared their admittedly arbitrary system to three other systems in place at that time, postulating that as their proposal was close to those in existence, it could be universally applied [113–115]. Crawford's system was based on water requirements dependent on surface area, relating the energy expenditure of a rat and a steer. However, interspecies energy expenditure is not comparable. Darrow and Pratt calculated energy expenditure based on nomograms (some from the 1920s) and systems on units/100 calories expended. Wallace related calorie requirements/kg to age, stating:

$$\text{Caloric need / kg} = 110 - 3 \times \text{patient's age}$$

His system was intended for patients under the age of 20 and weight less than 60 kg. Holland Segar manipulated much of their data, using at times only two babies, assuming the adult's diet is equivalent to cow's milk whereas an infant is closer to glucose and quoting mostly unpublished studies.

But based on these assumptions, protocols were developed that calculated deficits based on degree of trauma, insensible losses, and a host of other "variable" fluid decreases, all of which were to be replaced with crystalloids. Holliday and Segar's proposal evolved into the 4:2:1 "rule," which is still taught and found in major anesthetic and surgical textbooks (first 0–10 kg requires 4 ml/kg, next 11–20 kg 2 ml/kg, then >21 kg is 1 ml/kg). The explanation for the "rule" is that "it segments the curvilinear relationship between body weight and metabolic rate into 3 linear parts" [116]. Basically, the calculations assume:

1. Surface area is a good estimate of water expenditure.
2. Caloric expenditure can be based on age, weight, activity, and food intake (comparing a rat and a steer).
3. Urinary volume and insensible losses relate to age.

No account is made of neurologic, endocrine, pharmacologic, and cardiovascular status, or other pathologic conditions. The concept of preoperative deficit also enters the equation, especially now that patients are advised to drink water 2 h preoperatively. Moreover, laparoscopic techniques are more often used with less fluid loss.

Acceptance of less fluid administration perioperatively has been only slowly embraced. Fortunately, we are now seeing large randomized studies that endorse a more limited and goal-directed approach to IV fluid replacement [117]. While normal saline was the preferred fluid for years, more recently it has been associated

with hyperchloremic metabolic acidosis [118]. Colloid (hydroxyethyl starch) was touted as a fluid that would mantain intravascular volume as opposed to crystalloids that would quickly leave the vasculare space. Much of the early work on colloids was published by Joachim Boldt, a Grman anesthesiologist. Because of lack or Institutional Review Board approval in 89 or 102 of his studies combined with double publications, manipulation of demographics and outcome data, 96 of his papers were retracted starting in 1986 until 2017 [119]. Hydroxyethyl starch received a black box warning, However, newer studies suggest that such a labelling may not have been entirely warranted and addition of modest amounts of colloid with reduction of crystalloid administration is associated with better outcomes especially in promoting enhanced recovery strategies [120–123]. Moreover, rather than simply randomly infusing through large bore cannulae, both pleth variability index and pulse pressure variation offer a more precise measure of fluid administration [124, 125].

Conclusion

The history of fluid administration spans thousands of years with many twists and turns. From earliest times when disease was thought to be due to bad blood that had to be drained to times when copious fluids were given, now returning to a more restricted view, the story still evolves as the optimum fluid and most advantageous amounts are better understood but still not realized.

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The Revised Starling Principle and Its Relevance to Perioperative Fluid Management

2

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Abstract

The Starling Principle states that fluid movements between blood and the tissue are determined by differences in hydrostatic and colloid osmotic pressures between plasma inside the microvessels and fluid outside them. While experimental evidence has established the general validity of Starling's Principle, difficulties in interpreting it quantitatively became apparent when measurements of interstitial fluid (ISF) hydrostatic and colloid osmotic pressures became possible. The revised interpretation recognizes that since vessel walls are permeable to macromolecules, a static equilibrium resulting from the balance of pressures cannot be achieved. Colloid osmotic pressure differences between plasma and interstitial fluid depend on low levels of filtration in most tissues. Plasma volume is maintained as a steady state with fluid loss by filtration from plasma to ISF being roughly matched by fluid gains from lymph. The differences in colloid osmotic pressure that determine blood tissue fluid exchange are those across the ultra-filter in vessels walls, namely the glycocalyx on the luminal surface of vascular endothelium. The mean value of colloid osmotic pressure of the ISF in a tissue can differ considerably from its value on the interstitial side of the glycocalyx since macromolecules are excluded from the main pathways through the water-filled interstices in the glycocalyx available to water and small water-soluble solutes (the small pore pathway). The macromolecules enter ISF via the

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large pore pathway, which consist of very occasional openings through the endothelium and its glycocalyx (large pores) or vesicular transport. The transient changes in the rates of fluid exchange between blood and tissues are directly proportional to (linear with) transient changes in microvascular pressure. By contrast, in tissues where all the ISF is initially formed by an ultrafiltrate of plasma, the steady state levels of filtration from plasma to tissues are non-linear, being close to zero over the range of pressure below the effective colloid pressure differences and then, showing a sharp upward curvature which at higher pressures approximates closely to a straight line. In those tissues where the relation has been investigated in detail, the curve has the shape of an ice-hockey stick. The curvature (non-linearity) reflects the fact that the colloid osmotic pressure of the ultrafiltrate is dependent on filtration rate and ultimately upon the hydrostatic pressure difference. Since pulmonary capillary pressures are low, monitoring plasma colloid osmotic pressure during large crystalloid infusions may be useful in averting pulmonary edema.

Abbreviations (Where Greek characters are used, English name is given in brackets)

J_S	Solute flux
J_V	Fluid filtration rate
L_P	Hydraulic permeability (conductivity through) of microvessel wall
P	Hydrostatic pressure
P_C, P_I	Microvascular, interstitial hydrostatic pressures
P_a, P_V	Arterial, venous pressures
Π = (*pi*)	Colloid osmotic pressure
Π_P, Π_C, Π_I	Plasma, microvascular, interstitial (including sub-glycocalyx) colloid osmotic pressures
ΔP, $\Delta\Pi$ = (*delta P, delta pi*)	Hydrostatic and colloid osmotic pressure differences across glycocalyx
Ra, Rv	Pre-capillary and post-capillary resistance
σ = (*sigma*)	Membrane (osmotic) reflection coefficient
Σ = (*capital sigma*)	Summation
τ = (*tau*)	Mean transit time.

Key Points

1. Fluid movements between plasma and interstitial fluid are determined by differences in hydrostatic and colloid osmotic pressures across the glycocalyx on the luminal side of the endothelial cells. These differences in pressures are not the same as (and may differ considerably from) the differences between their mean values in plasma and interstitial fluid.

2. A static equilibrium set by a balance of hydrostatic and osmotic pressures across the glycocalyx cannot be maintained. Because microvascular walls are permeable to macromolecules, the colloid osmotic pressure difference depends on continuous filtration through the glycocalyx. In most capillaries and venules, absorption of fluid from tissues into blood is transient and reverts to low levels of filtration in the steady state. Continuous fluid uptake from tissues to blood can only occur when a significant fraction of the interstitial fluid is formed as a protein-free secretion from a nearby epithelium (e.g., intestinal mucosa, kidney cortex, and medulla) or when there is a steady flow of interstitial fluid through the tissue (e.g., lymph flowing through of lymph nodes is absorbed into the nodal microcirculation).
3. Whereas transient changes in fluid transport across microvascular walls are directly proportional to step changes in hydrostatic pressure when plasma and interstitial fluid colloid osmotic pressure are constant (a linear relation), steady state changes in fluid transport with changes in pressure are curvilinear (hockey stick shape). For increments of pressure between zero and the plasma colloid osmotic pressure, Πp, increases of steady state filtration are very small but as pressure reaches Πp, steady state filtration rates increase rapidly and approximate asymptotically to the hydraulic permeability.
4. Transient periods of fluid exchange following a step change in microvascular pressure vary considerably from tissue to tissue. A steady state is reached within a few minutes in lung, mesentery, and intestinal tract, but may take more than 30 min in skeletal muscle.
5. The hockey stick shape of the curve relating steady state fluid filtration to microvascular pressure predicts that dilution of the plasma proteins by intravenous infusion of crystalloid solutions increases fluid filtration when microvascular pressures are equal to or above plasma colloid osmotic pressure, but have little effect on steady state filtration rates when microvascular pressure is well below this (as in shock). Because pulmonary capillary pressures (Pc) are low, it suggests why moderate reductions of plasma colloid osmotic pressure by crystalloid infusions do not precipitate pulmonary edema but reducing the colloid osmotic pressure to levels just above Pc may do so.

Introduction

Intravenous fluid therapy dates from the First World War when the military surgeons were confronted by large numbers of wounded soldiers with surgical shock. Blood transfusion was experimental and difficult to carry out close to the front and the beneficial effects of infusion of crystalloid solutions (0.9% saline or 2% sodium bicarbonate solution) upon arterial blood pressure were short-lived. Following experiments on anesthetized animals by William M. Bayliss [1], the Medical Research Committee (MRC) on wound shock recommended that infusions of 0.9% saline should contain a macromolecular solute. As collaborator, colleague, and brother-in-law of Ernest H. Starling, Bayliss was, of course, familiar with Starling's

hypothesis that fluid was retained in the circulation by a balance of hydrostatic pressures and colloid osmotic pressures across the walls of capillaries [2]. In 1918, intravenous infusions of solutions of 7% gum Arabic in isotonic saline, which has the same colloid osmotic pressure and viscosity as plasma, were used to resuscitate wounded soldiers at the casualty clearing stations. It was reported to be much more effective in reducing mortality than infusions of 0.9% saline alone. Unfortunately, these reports were mainly anecdotal [3].

Although subsequent adverse reactions to artificial colloids (gum Arabic, gelatin, and dextrans) inhibited their use, it was widely believed that in the absence of blood for transfusion, infusion of plasma or isotonic salt solutions containing colloids were more effective than infusions of crystalloid solutions alone. It therefore came as a surprise when it was reported that trauma and burn patients had a lower mortality when initially treated with crystalloid infusions than when plasma or albumin solutions had been used. While the infusion of a given volume of a crystalloid solution into healthy volunteers left the circulation more rapidly than an equal volume of colloid solution, this difference was less clear when carried out in patients suffering from blood loss. The validity of the conclusions from the earliest reports were challenged and the subsequent debate—the colloid crystalloid controversy—is considered in other sections of this book.

In 2012, Woodcock and Woodcock [4] pointed out that developments over the previous 30 years in understanding microvascular fluid exchange offered a rationale for the use of crystalloid infusions in maintaining plasma volume in patients. This chapter describes these fundamental ideas, which have been called "the revised Starling Principle". First, however, we consider Starling's hypothesis as it was originally stated, the evidence for it, and how it has been misinterpreted, before moving on to discuss these more recent developments. In this chapter, the important role of the glycocalyx in fluid exchange will be discussed, but its structure, permeability, and other properties are considered in the next chapter.

Starling's Hypothesis and Its Traditional Interpretation

Starling became interested in the mechanism of lymph formation in the early 1890s. At that time, it was widely believed that lymph (tissue fluid) was formed as an active secretion of the capillary walls. Although it had been proposed that lymph was formed as an ultrafiltrate of plasma, apparently convincing evidence for lymph's active secretion had been published by Heidenhain in 1890. In 1892, Starling spent several months working with Heidenhain in Breslau (now the Polish city of Wroclaw) familiarizing himself with Heidenhain's experiments and his methods. When he returned to London later that year, he started a series of experiments in which he hoped to establish the secretory process more convincingly and show how it was regulated. The first set of experiments were carried out in collaboration with Bayliss. Far from providing convincing proof that lymph was formed as a secretion, Bayliss and Starling demonstrated that when Heidenhain's experiments were carefully controlled, they revealed powerful

evidence that lymph was formed by the ultra-filtration of plasma through the capillary walls (see [5, 6] for reviews).

At that time, it was believed that whereas fluid might be secreted from plasma into the tissues, tissue fluid could only be returned to the blood via the lymph. Convinced that interstitial fluid (ISF) was formed by the ultrafiltration of plasma, Starling now suspected that fluid could move directly from the tissues into the plasma. He assembled various lines of evidence for this, demonstrating that the fall in hematocrit after hemorrhage could not be accounted for either by an increased return of lymph from the thoracic duct to the blood or by increased uptake of fluid from the gastrointestinal tract [2]. In experiments on anesthetized dogs, where he perfused the isolated circulation of the hind limb with defibrinated blood, he then showed that a volume of 1% solution of sodium chloride injected into the muscles of the limb could be absorbed into the blood that circulated through it. An equivalent volume of plasma could not be absorbed and remained in the tissues [2]. He made the first measurements of the colloid osmotic pressure of plasma and found its value lay in the range that Bayliss and he had estimated for capillary pressures in anesthetized dogs. Here he had convincing evidence that fluid could flow directly from the tissues into the circulating blood and he proposed that the driving force for this was the difference between the colloid osmotic pressure of the plasma and that of the interstitial fluid [2].

Box 2.1 gives quotations from Starling's 1896 paper and reveals his insight in arguing that the difference in osmotic pressure between the plasma and the interstitial fluid would be proportional to the work done in forming the interstitial fluid from the plasma by ultrafiltration. He also saw his hypothesis as the principle way in which the blood volume was regulated.

Box 2.1 Starling's Hypothesis in His Own Words

"…the osmotic attraction of the serum for the extravascular fluid will be proportional to the force expended in the production of this latter, so that, at any given time, there must be a balance between the hydrostatic pressure of the blood in the capillaries and the osmotic attraction of the blood for the surrounding fluids."

"With increased capillary pressure there must be increased transudation until equilibrium is established at some higher point, when there is more dilute fluid in the tissue-spaces and therefore a greater absorbing force to balance the increased capillary pressure."

"With diminished capillary pressure there will be an osmotic absorption of saline from the extravascular fluid, until this becomes richer in proteids; and the difference between its (proteid) osmotic pressure and that of the intravascular plasma is equal to the diminished capillary pressure."

"Here then we have the balance of forces necessary to explain the accurate and speedy regulation of the circulating fluid."

From E. H. Starling *J. Physiol*. 1896 [2].

Although Starling reported improvements in his method for measuring the colloidal osmotic pressure of plasma and appreciated its importance in limiting glomerular filtration in the kidney, he published no further experimental work to support his hypothesis. He did, however, describe his ideas in the lectures that he gave and incorporated it into the textbooks of physiology that he wrote. His hypothesis was not accepted immediately and, as late as 1912, it was referred to in one influential textbook that doubted that it was the likely explanation of blood-tissue fluid exchange [6]. Some influential figures, however, were soon to be convinced. In his Silliman lectures on the capillary circulation, Krogh [7] discussed Starling's hypothesis at length but noted that nothing new had been added to the subject since Starling's paper.

Inspired by Krogh's comments, a medical student at the University of Pennsylvania, Eugene Landis, developed a method for measuring the hydrostatic pressure in single capillaries in the frog mesentery by direct micro-puncture [8]. He also developed an ingenious method for estimating the rate of fluid filtration and absorption through the walls of single capillaries. When he plotted values of the fluid filtration or absorption rates through the walls of single capillaries against the hydrostatic pressures inside them, he found a strong positive linear correlation (Fig. 2.1) [8]. When he could detect no fluid movements across the walls of a vessel,

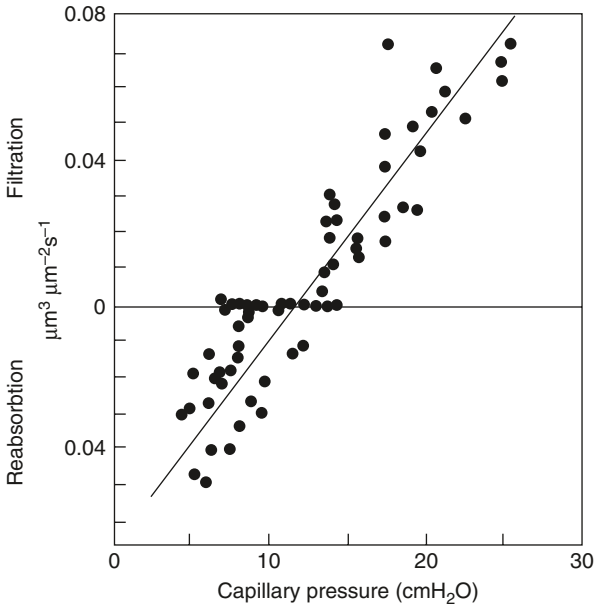

Fig. 2.1 The relationship between fluid movements through the walls of different capillaries in frog mesentery and the capillary's pressure as determined by Landis in 1927. Data re-plotted from original in *American Journal of Physiology*. (Adapted with permission of the American Physiological Society, from Michel CC. Fluid movements through capillary walls. In: *Handbook of Physiology. The Cardiovascular System.,* vol 4, *Microcirculation,* part 1, edited by Renkin EM, Michel CC, Geiger SR. American Physiological Society. 1984. Bethesda MA USA. Chap. 9, pp. 375–409

he found the capillary pressure lay within a range of values that had been measured for the colloid osmotic pressure of plasma of the same species of frogs. Landis indicated that his findings could be summarized as the equation of a linear relation between filtration rate and capillary hydrostatic pressure [8]. Using modern symbols to represent the various terms, this is:

$$\frac{J_V}{A} = L_P\left[\left(P_C - P_I\right) - \left(\Pi_C - \Pi_I\right)\right] \tag{2.1}$$

where J_V/A = filtration (+) and absorption (−) rates per unit area of capillary wall, L_P = the hydraulic permeability or conductivity of the capillary wall, P_C and P_I are the hydrostatic pressures in the capillary and the interstitial fluid respectively and Π_C and Π_I are the colloid osmotic pressures of the capillary plasma and the interstitial fluid respectively. P_C, P_I, Π_C and Π_I are often referred to as the Starling pressures.

These findings were both qualitative and quantitative evidence for Starling's hypothesis and immediately recognized as such, with Krogh rewriting the sections on the fluid exchange and permeability for the new edition of his monograph on capillaries [9].

After qualifying in medicine, Landis travelled to Europe and spent the winter of 1928/1929 in London in the laboratory of Sir Thomas Lewis. Here he measured the pressures in the capillary loops of the fingernail beds of healthy human volunteers [10]. With the subject's hand at heart level, the pressure in the arteriolar limb of the base of the capillary loops had a mean value of 32 mm Hg and in the venous limb a mean of 12 mm Hg. At the halfway point at the tip of loop, its mean value was 25 mm Hg. The colloid osmotic pressure of plasma of healthy volunteers is approximately 25 mm Hg, so this gradient of pressure along the capillaries was consistent with Starling's speculation that fluid was filtered from the plasma into the tissues at the arteriolar end of capillary beds and absorbed from the tissue spaces at the venous end [11]. (This conclusion, however, assumed that both the hydrostatic and colloid osmotic pressures of the interstitial fluid were zero).

From London, Landis moved to Copenhagen where he joined Krogh's laboratory. Here he measured capillary pressure in different tissues of the frog and small mammals. Again, he found capillary hydrostatic pressure lay in the range of values for the plasma colloid osmotic pressure measured in these different species. Not only did these findings provide further support for Starling's hypothesis, they also were consistent with Starling's conjecture [11] that fluid was lost from the circulating plasma into the tissues as it flowed through the arterial side of the microcirculation and regained fluid as the plasma flowed through the venous side. (Once again, the assumption here is that P_I and Π_I are zero.) This idea could be shown as a diagram, which was soon the standard way of teaching blood-tissue fluid exchange to medical students (Fig. 2.2). In a very influential review, Landis and Pappenheimer [12] attempted to estimate the daily flows of fluid between the arterial and venous sides of the microcirculation and the tissues. Although they recognized that microvascular walls were finitely permeable to macromolecules, they guessed that their concentrations in the interstitial fluid were very low. Although their figures have been very widely quoted, the authors themselves were cautious about conclusions

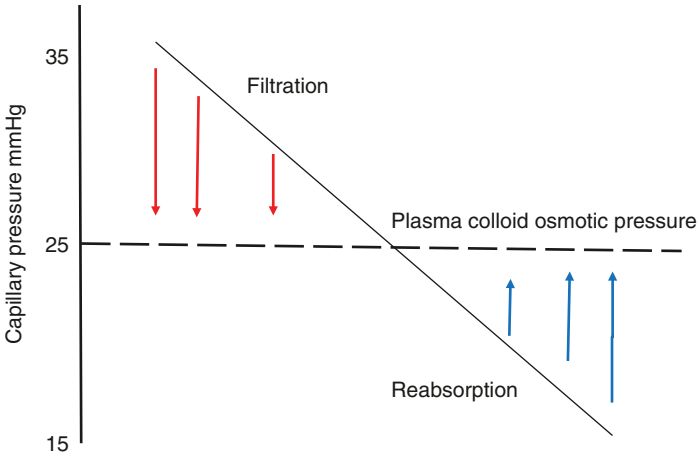

Fig. 2.2 Standard model of blood-tissue fluid exchange where filtration is shown as occurring in the upstream section of an exchange vessel where ΔP is greater than the plasma colloid osmotic pressure, and absorption is downstream where ΔP is lower than the plasma colloid osmotic pressure

drawn from them; Landis, both in this review and in his earlier writings, was well aware that the simple picture might be complicated by differences in the height of tissues relative to the heart in larger animals and particularly in humans. It was later shown that during quiet standing, P_C in the capillaries of the toes of human subjects could be 100 mm Hg or more than they were in the fingers of the same individual when the hands were held at heart level [13, 14]. As Levick [15, 34] has pointed out, there is no evidence for the textbook picture of simultaneous fluid filtration from the arterial half and fluid uptake into the venous half occurring in the microcirculation of any tissue, with the possible exception of the vasa recta of the renal medulla where other forces are involved.

Quite apart from direct measurements of capillary pressure in animals and humans, Landis's most important legacy was his demonstration of the linear relation between filtration rates and capillary pressure. He saw its importance in human physiology, developing a plethysmograph while in Krogh's laboratory for estimating fluid filtration rates in the forearm of human volunteers; he continued this approach when he returned to the United States. Here Landis and Gibbon [17] were able to show that increases in venous pressure were accompanied by increases in the rate of swelling of the tissues resulting from greater rates of ultrafiltration of fluid from the microvascular blood. If one were to assume a proportionate relationship between increments in the venous pressure and increments in the mean microvascular pressure, then their findings were consistent with Starling's Principle as expressed in eq. (2.1). More than 10 years were to elapse before the relations between arterial and venous pressures and the mean microvascular pressure in a tissue were clearly defined. Establishing these relations allowed investigators to demonstrate Starling's Principle in entire microvascular beds.

Microvascular Pressures, Vascular Resistance, and Fluid Exchange in Organs and Tissues

The relations between the mean microvascular pressure in an organ or tissue and the co-existing arterial and venous pressures was spelt out clearly by Pappenheimer and Soto-Rivera in 1948 [18]. Arguing that if the net rate of loss or gain of fluid by the blood flowing through a tissue is negligible compared with the blood flow itself, the flow of blood into a microvascular bed from the arteries is equal to the flow out into the veins. This means the blood flow from arteries to capillaries is equal to the flow of blood from the capillaries into the veins. Since flow through a section of the circulation may be expressed as the ratio of the fall in pressure across that section to the resistance to flow through the vessels, the fall in pressure from the arteries to the capillaries divided by the pre-capillary resistance should equal the fall in pressure between the capillaries and the veins divided by the post-capillary resistance. If P_a = arterial pressure, P_C = mean microvascular pressure, P_V = venous pressure and *Ra* and *Rv* are the precapillary and post-capillary resistances of the circulation, then:

$$Flow = \frac{Pa - Pc}{Ra} = \frac{Pc - Pv}{Rv},$$

which may be re-arranged as:

$$Pc = \frac{Pa + \left(\frac{Ra}{Rv}\right) Pv}{1 + \frac{Ra}{Rv}} \tag{2.2}$$

Pappenheimer and Soto-Rivera [18] worked with isolated perfused limbs of cats and dogs, which they weighed continuously to measure fluid accumulation or fluid loss from the tissues. Adjusting the arterial and venous pressures until the limb neither gained fluid from the blood nor lost it to the circulation, they argued that the mean capillary pressure in the microcirculations of the limb balanced the other pressures in the Landis-Starling equation [see eq. (2.1)] under these conditions, which they called the iso-gravimetric state. Then by adjusting the arterial and venous pressures they were able to vary the blood flow through the limb and hold the weight of the limb constant. They found that under iso-gravimetric conditions, blood flow increased linearly with reduction in the venous pressure. Arguing that in the iso-gravimetric state, the mean capillary pressure was constant, they used the linear relation between the fall in venous pressure and blood flow and determined the mean capillary pressure by backward extrapolation of the values of venous pressure to its value at zero flow when capillary pressure and venous pressure were equal. With a set of values of P_a, P_V, and P_c they could calculate *Ra/Rv* from eq. (2.2). Knowing the value of *Ra/Rv,* they could now calculate the values of P_c from the arterial and venous pressures when the limb was no longer in an iso-gravimetric state. Following this protocol, Pappenheimer and Soto-Rivera [18] were able to establish (in a mammalian preparation) nearly all the predictions made by Starling.

They were also able to demonstrate the linear relation between filtration and fluid absorption rates and mean capillary pressure (eq. 2.1) seen by Landis in frog capillaries [8]. Also, by varying the protein concentration of the plasma and adjusting the arterial and venous pressures, they showed that the mean capillary pressures, which were required to prevent net fluid gain or loss to or from the tissues, approximated very closely to the colloid osmotic pressures of the perfusates. These results suggested that, in their isolated perfused limb preparations, the interstitial hydrostatic and colloid osmotic pressures were small, being of the order of 1 to –3 mm Hg. It seemed that Starling's hypothesis had been emphatically confirmed.

The physiological importance of eq. (2.2), was demonstrated in a series of studies by Folkow, Mellander, Öberg and their colleagues in the 1960's [19–21]. They demonstrated that, in skeletal muscle, sympathetic stimulation increased R_a/R_v, leading to a fall in P_c and a shift of fluid from the tissues to the blood.

The Osmotic Reflection Coefficient

A new conceptual interpretation of osmotic pressure measurements, based on the thermodynamics of the steady state, was introduced in 1951 by A. J. Staverman [22]. He concluded that the full theoretical osmotic pressure of a solution, Π, as defined by van't Hoff (= RTC, where R = the universal gas constant, T = absolute temperature, and C = molal concentration of solute in the solution) can only be measured across a perfectly semi-permeable membrane; i.e., a membrane that is completely impermeable to the solute while being permeable to the solvent. If the membrane is permeable to the solute, the effective osmotic pressure difference across it, $\Delta\Pi$, is reduced to a value of $\sigma\Delta\Pi$. The coefficient σ is the reflection coefficient of the membrane to the solute and is a measure of the relative ease with which the solute and the solvent of a solution may pass through the membrane. For an ideal solution, σ may be defined either as the fraction of its total osmotic pressure that may be exerted by a solution across the membrane, or the fraction of solute that is separated from its solution as it is filtered through the membrane in the absence of a concentration gradient across the membrane or at an infinitely high filtration rate. The equivalence of these definitions can be appreciated intuitively by considering the osmotic pressure of a solution as the pressure that opposes its ultra-filtration through a membrane. The fraction of solute molecules that is reflected at the upstream surface of the membrane during ultrafiltration represents that fraction of the osmotic pressure of the solution opposing filtration. (This is like Starling's insight that the "attraction of the plasma for the extravascular fluid will be proportional to the force expended in the production of this latter"; see Box 2.1). If the membrane is completely impermeable to the solute but permeable to the solvent (i.e., a truly semi-permeable membrane) σ of the membrane to the solution is 1.0 and the full value of the solution's osmotic pressure opposes its ultrafiltration. If, on the other hand, the concentration of the solution leaving the downstream surface of the membrane during ultrafiltration is unchanged from that entering at its upstream surface, the membrane is unselective as an ultra-filter to the solution, $\sigma = 0$ and the

solution's osmotic pressure will not oppose its filtration. This equivalence of the definition of reflection coefficient in terms of osmotic pressure and ultra-filtration assumes that the osmotic pressure of a solution is directly proportional to the fraction of the solute molecules in the solution. This is true only for "ideal" solutions, but is a good approximation for dilute solutions where the molecular size of the solute is comparable with that of the solvent; i.e. dilute solutions of urea, glucose, and sucrose where there is a linear relation between solute concentration and osmotic pressure. For macromolecules, such as the plasma proteins, the osmotic pressures of their solutions rise more rapidly with increasing concentration, and the equivalence between the osmotic reflection coefficient and the ultra-filtration reflection coefficient is only approximate.

Because the reflection coefficients of the plasma proteins responsible for its colloid osmotic pressure are high (≥ 0.9) at the walls of microvessels in most tissues, the concept of the reflection coefficient appears in most accounts as a minor modification of eq. (2.1), i.e.:

$$\frac{J_V}{A} = L_P\left[\left(P_C - P_I\right) - \sigma\left(\Pi_C - \Pi_I\right)\right] \tag{2.3}$$

Equation (2.3) is a useful way of representing microvascular fluid exchange but, strictly speaking, it is inexact. The colloid osmotic pressure of the plasma is the sum of the products of the osmotic pressures and their reflection coefficients of all the solutes in the plasma and should be written as $\Sigma\sigma\Pi_i$ and differences of colloid osmotic pressure across microvascular walls as $\Sigma\sigma_i\Delta\Pi_i$ where subscript i represents the individual solutes that contribute to the effective osmotic pressure differences. Equation (2.3) is more accurately written as:

$$\frac{J_V}{A} = L_P\left(\Delta P - \sum_i \sigma_i \Delta\Pi_i\right) \tag{2.4}$$

where $\Delta P = P_C - P_I$.

Further development of the theory by Kedem and Katchalsky [23] led to a much clearer understanding of the relations between the rates of microvascular fluid and solute exchange, pressure and solute concentration differences and the permeability coefficients. Two examples are illustrated in Fig. 2.3 in terms of the relations between filtration rates and microvascular pressure (the Landis diagram, Fig. 2.1). Figure 2.3a shows an experiment where a single capillary has been perfused with two different Ringer's solutions [24]. The first contained 80 g/l serum albumin, but in the second solution the albumin concentration was only 25 g/l. The initial rates of fluid exchange intersect the pressure axis at approximately 30 cm H_2O when the albumin concentration is high and at approximately 12 cm H_2O when albumin concentration is low. The shift represents the difference in the effective colloid osmotic pressures ($\sigma\Delta\Pi$) exerted by the two solutions. In Fig. 2.3b, a single rat venule has been perfused *in situ* with same solution throughout an experiment [25]. Here, however, the initial measurements of filtration rates were made under control conditions. The mesentery was then treated with histamine and over the following few

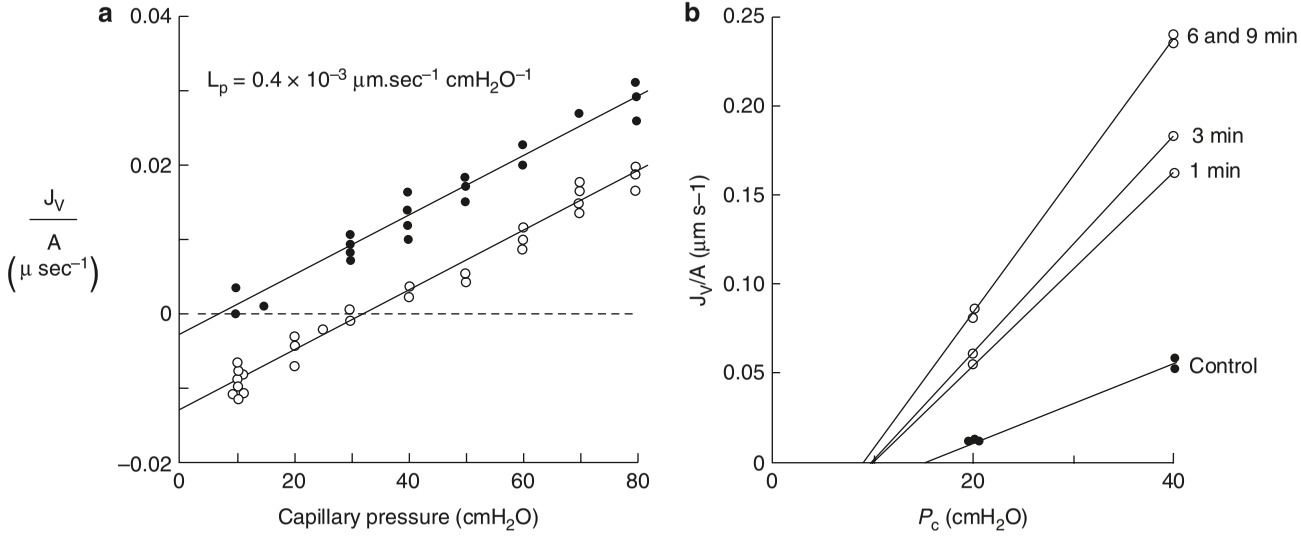

Fig. 2.3 Two experiments carried out on single perfused capillaries to illustrate the uses of the classical interpretation of Starling's principle when data are plotted in the way introduced by Landis. (**a**) The relation between fluid movements per unit area (J_V/A) and capillary pressure through the walls of a single capillary first when perfused with a Ringer solution containing 8% serum albumin (right hand line) and then with a solution containing 2.5% serum albumin. Note how reducing the albumin concentration shifts the relation to the left as the effective colloid osmotic pressure opposing filtration is reduced but the slope of the relation (hydraulic permeability) is unchanged. (Reprinted with permission of the Alfred Benzon Foundation, from Michel CC. The flow of water through the capillary wall. In: Ussing HH, Bindslev N, Lassen NA, Sten-Knudsen (eds). Alfred Benzon Symposium 15: Water Transport Across Epithelia. Copenhagen: Munksgaard, 1981: 268–279). (**b**) Changes in the relationship between fluid filtration rates per unit area (J_V/A) through the walls of a rat mesenteric venule at different microvascular pressures (P_C) before and during exposure to histamine, which increases both hydraulic permeability and permeability to macromolecules. Note how this is reflected in the increase in the slope (increased hydraulic permeability) and the leftward shift of the intercept (increased permeability to macromolecules). The numbers against each line are minutes of exposure to histamine. (Reprinted with permission from Michel CC, Kendall S. Differing effects of histamine and serotonin on microvascular permeability in anaesthetized rats. J Physiol 1997. 501: 657–662)

minutes the filtration rate rose and its relation to capillary pressure was shifted to the left indicating that the reflection coefficient of the vessel wall to the macromolecules in the perfusate was reduced. Note also that the slope of the relation between filtration rate and pressure was increased, indicating that the hydraulic permeability was increased also.

The introduction of the reflection coefficient had another important implication for the interpretation of Starling's Principle that was not immediately recognized. Until this time, it had been assumed that an equilibrium could be established between the osmotic and hydrostatic pressures differences across microvascular walls; i.e., the pressures in eq. (2.1) balance and hence zero fluid flow. The reflection coefficient was a signal that, even when the pressures were unchanging, there was no equilibrium but a steady-state could exist. This steady state was maintained by a small but steady flow of fluid from plasma to interstitial fluid to lymph. The significance of this was not appreciated for another 30 years.

The Hydrostatic and Colloid Osmotic Pressures of the Interstitial Fluids

Because the few direct measurements of capillary hydrostatic pressure that had been made before 1963 had values similar to the plasma colloid osmotic pressures and because lymph flow was low in tissues other than those of the liver and gastrointestinal tract, it was assumed that net fluid movements across microvascular walls were very low and the interstitial fluid hydrostatic and colloid osmotic pressures were small. It seemed possible that a small positive interstitial hydrostatic pressure offset the interstitial colloid osmotic pressure. The significant levels of plasma proteins found in the lymph from most tissues were believed to reflect the interstitial fluid surrounding the venules and venular capillaries where microvascular hydrostatic pressures were low. Attempts to measure interstitial fluid hydrostatic pressure by inserting a fine needle into the tissues suggested that its value was close to or slightly greater than atmospheric pressure.

In 1963, Guyton reported a novel method of estimating interstitial hydrostatic pressure (Fig. 2.4) by measuring the pressure of the fluid that accumulated in a capsule, which had been implanted and allowed to heal into the subcutaneous tissues of a dog [26]. The values he measured were between 2 and 7 mm Hg below atmospheric pressure. In later experiments, Pi measured in capsules chronically implanted in the dog lungs were found to be as low as 9–11 mm Hg below atmospheric pressure. Although soon reproduced in other laboratories, the sub-atmospheric (or negative) pressures were very controversial and there was great interest and speculation as to how they arose. Toward the end of the decade, Scholander et al. [27] reported somewhat smaller (less negative) sub-atmospheric pressures in interstitial fluids using wicks of cotton fibers saturated with isotonic saline solutions to make contact between the tissue fluids and the experimenter's manometer. Controversy as to whether the sub-atmospheric pressures were artefacts of the measuring techniques was heightened when direct measurements using the servo-nul micropipette

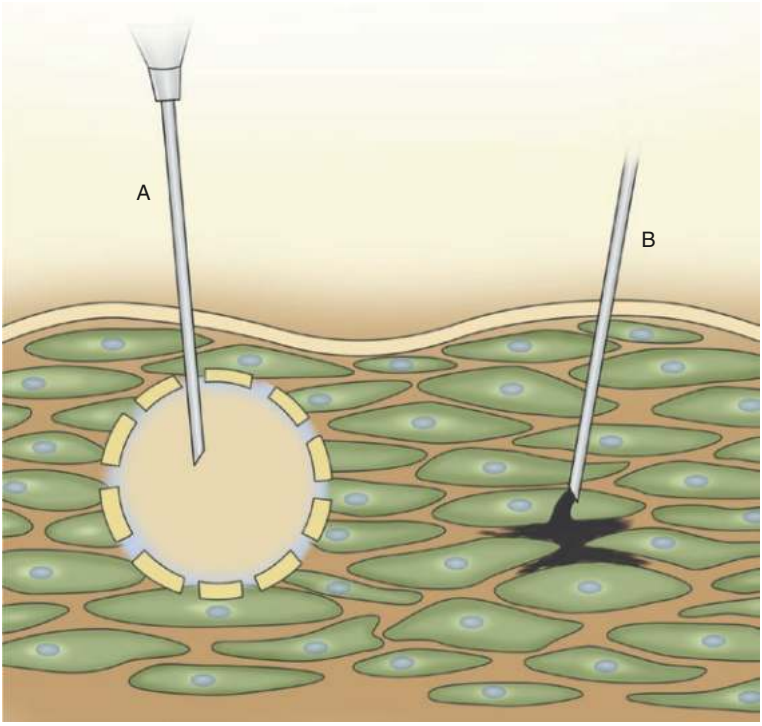

Fig. 2.4 Schematic diagram to illustrate the Guyton capsule (**a**) and the Aukland-Reed wick in needle (**b**) methods for measuring interstitial hydrostatic pressure and mean interstitial colloid osmotic pressure. Interstitial fluid hydrostatic and colloid osmotic pressures have also been measured in joint cavities and interstitial hydrostatic pressure has been measured using the servo-nul micropipette technique

technique, which had been developed to measure pressure in small blood vessels, yielded P_I values around atmospheric pressure [28].

Fluid from the implanted capsules could be removed and analyzed for its protein content and colloid osmotic pressure. A careful study by Aukland and Fadnes [29] showed that interstitial fluid protein concentration could also be obtained from implanted wicks. The values of interstitial colloid osmotic pressure, Π_I, were of the order of 10 mm Hg in subcutaneous tissues of rats and dogs. If the colloid osmotic pressure of the plasma was 25 mm Hg, this indicated that the osmotic pressure difference available to move fluid from the tissues into the plasma was only 15 mm Hg. At the same time, the sub-atmospheric values of P_I would add to the mean capillary pressure and increase the hydrostatic pressure difference favoring filtration of fluid from plasma to tissues. The direct measurements of capillary pressure, which approximated to the plasma colloid osmotic pressure and had appeared as strong evidence for a "Starling equilibrium," now seemed to suggest the differences between the hydrostatic and colloid osmotic pressures across capillary walls

amounted to 10 mm Hg or more. These implications for the concept of a balance of pressures, however, were initially overshadowed by the controversy over the measurement of P_I and what it represented.

Later, as fluid exchange came to be considered in the light of the new measurements of P_I and Π_I, the inconsistency between the few direct measurements of capillary hydrostatic pressure and the other variables of the Starling equation in the resting state led to the idea that the mean capillary pressures that determined fluid exchange were well downstream in the venular section of the microvascular beds rather than at the mid-capillary level [30–33]. The concept was reinforced by Chen et al. [31] who estimated that in order to balance the hydrostatic and colloidal osmotic pressures between the capillary blood and the interstitial fluids, the mean capillary pressure in the limb of a dog had to be as low as 12.2 mm Hg when Π_C was greater than 20 mm Hg. It was observed, however, that with small increments in interstitial fluid volume, P_I rose rapidly to zero (atmospheric pressure) and remained there as the interstitial fluid volume was increased, only rising significantly above zero after the tissues were conspicuously edematous. This, together with the older observation that increases in filtration into the tissues are accompanied by increases in lymph flow and reductions in lymph protein concentration, led to the idea that changes in the interstitial hydrostatic pressure and colloid osmotic pressure acted to minimize edema formation [31–33].

The idea that low values of the mean microvascular pressures could balance the other pressures of the Starling equation was challenged by Levick in a review published in 1991 [34]. By this time, values for the interstitial hydrostatic and colloidal osmotic pressures had been determined in many different tissues and in some cases there had also been concomitant measurements of the venular or venous pressures. Levick estimated the mean microvascular hydrostatic pressure, $P_C\,(0)$, that would balance the plasma colloid osmotic pressure and the interstitial pressures by rearranging eq. (2.3); i.e.:

$$P_C(0) = \sigma\left(\Pi_C - \Pi_I\right) - P_I \tag{2.5}$$

He then compared these values of $P_C\,(0)$ with the measured values of venous or venular pressure. His findings supplemented by a few additional values, are shown as a graph relating P_V to $P_C\,(0)$ in Fig. 2.5 [34]. Only in the intestinal mucosa and the kidney, two tissues whose specialized function is to deliver fluid and solutes into the circulation, are values of P_V below those estimated for $P_C\,(0)$. In other tissues, the higher values of P_V than $P_C\,(0)$ suggest significant levels of fluid filtration. In most of these tissues, the vascular endothelium of the capillaries and venules is continuous (non-fenestrated) and where estimates of the hydraulic permeability have been made, minimal fluid filtration rates can be calculated using the pressure differences shown in Fig. 2.5. These greatly exceed measured lymph flows from these tissues. Indeed, so large was this discrepancy that the hypothesis suggested to resolve it has been called the "revised" Starling Principle [6, 35, 36]. It involves a closer look at microvascular permeability and microvascular fluid exchange.

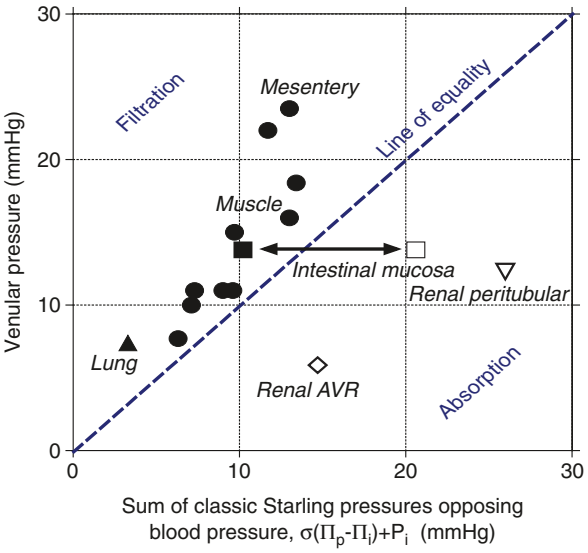

Fig. 2.5 The hydrostatic pressures in veins and venules of different tissues plotted against the sum of the pressures in those tissues that oppose fluid filtration. The Starling equilibrium or balance would be present if points lay on the line of equality. The points based on data from most tissues lie above this line indicating significant levels of fluid filtration into the tissues. Only points representing renal cortex and medulla and intestinal mucosa during absorption lie below the line. Note how the point for the intestinal mucosa lies above the line when in a non-absorptive state. (Reprinted with permission from Levick JR, Michel CC. Microvascular fluid exchange and revised Starling principle. Cardiovascular Res. 2010; 87:198–210)

Steady State Fluid Exchange Between the Plasma and the Tissues

The extension of the Starling Principle has two components. The first is the recognition of the relations between fluid exchange and microvascular pressure under steady state conditions. The second component is the hypothesis to account for the much lower filtration rates in tissues such as muscle than those that are predicted from the mean values of the capillary hydrostatic and plasma colloid osmotic pressures and the mean values of hydrostatic and colloid osmotic pressures of the interstitial fluid. In this section we consider the steady state relations.

Earlier it was noted that the concept of the reflection coefficient meant that one could no longer think in terms of the difference in hydrostatic and osmotic pressures across microvascular walls reaching an equilibrium. If microvascular walls are permeable to both proteins and water, the only true equilibrium that could be reached would be one where there were no differences in hydrostatic pressure or in protein concentration (and hence no difference in osmotic pressure) across the membrane. If a difference in hydrostatic pressure across microvascular walls is established with a higher pressure in the plasma, fluid from the plasma is filtered into the tissues and if the water molecules are able to pass more rapidly through the microvascular walls

Box 2.2 Diffusion and Convection

Diffusion is the process whereby molecules initially confined to one part of a system are able to distribute themselves throughout the system by their thermal motion. Thus, in an aqueous solution, which is concentrated in part of a region, the random kinetics of the solute and water molecules lead to net movements of solute from regions of initially high concentration to those where the concentration was initially low, exchanging places with water molecules, which show a net movement in the opposite direction. Essentially it is a mixing process on a molecular scale so that gradients of concentration are dissipated and concentration becomes uniform throughout the system with no change in volume.

Convection in this context refers to net movements of the solution (both solute and water moving together) from one part of the system to another. It is sometimes referred to as "bulk flow" or "solvent drag."

than protein molecules, a concentration difference of plasma protein across the membrane is established. The presence of a concentration difference stimulates a net diffusion of solute from plasma to tissue fluid so the maintenance of the concentration difference involves a constant race between the filtration of water molecules (convection) and the convective transport and diffusion of the solutes (Box 2.2). It requires a constant flow of fluid from the plasma into the interstitial spaces to maintain the difference in colloid osmotic pressure across microvascular walls. If the hydrostatic pressure difference is held constant for sufficient time, a steady state concentration difference develops, its value being determined by the filtration rate (and its relation to the hydrostatic pressure difference) and the relative permeability of microvascular walls to water and macromolecules.

Starling (see Box 2.1) argued that an increase in the difference in hydrostatic pressure across microvascular walls would increase filtration of fluid from plasma into the interstitial spaces concentrating the proteins in the plasma and diluting those in the interstitial fluid, so increasing the osmotic pressure difference opposing filtration. This in turn curbs the filtration rate until the latter is brought to a halt when hydrostatic pressures and osmotic pressures are equal. Starling believed at this stage a new equilibrium would be achieved, but this is not possible if microvascular walls are permeable to macromolecules.

In the absence of continued filtration, diffusion of macromolecules will dissipate their concentration difference, reducing the colloid osmotic pressure difference and allowing filtration to increase once again. For a given difference in hydrostatic pressure across the microvascular wall, however, there is a steady state difference in colloid osmotic pressure that minimizes the filtration rate. The reflection coefficient, σ, for macromolecules is high at most capillary walls and when ΔP falls below the effective osmotic pressure difference, $\sigma\Delta\Pi$, filtration in the steady state may be very low.

Figure 2.6a shows the way in which the concentration of proteins in the filtrate passing through microvascular walls varies with filtration rate when the plasma

concentration is constant. Because the reflection coefficient of microvascular walls to macromolecules is high (≥ 0.90) the protein concentration in the filtrate falls rapidly at first as filtration rate is increased and levels off to a value of less than a tenth of the plasma concentration approaching an asymptote equal to $(1\text{-}\sigma)$ multiplied by the plasma concentration. A derivation of this curve from first principles, showing its dependence on the permeability properties of microvascular walls, is given in the Appendix to this chapter.

Figure 2.6b shows how the effective osmotic pressure difference across microvascular walls varies with the filtration rate when the plasma protein concentration is held constant under steady state conditions. As one might expect from Fig. 2.6a, the effective osmotic pressure difference rises to a maximum value that is just less than the osmotic pressure of the plasma. Because the effective osmotic pressure difference, $\sigma\Delta\Pi$, is dependent upon the filtration rate, which in turn is dependent on the differences between the hydrostatic and colloid osmotic pressures, $(\Delta P - \sigma\Delta\Pi)$, the steady state relations between fluid movements and ΔP do not follow the simple linear relation that might be expected from eq. (2.3) or those shown in Figs. 2.1 and 2.3. The steady state curve predicted from the basic theory is markedly curvilinear and is shown in Fig. 2.7a [38].

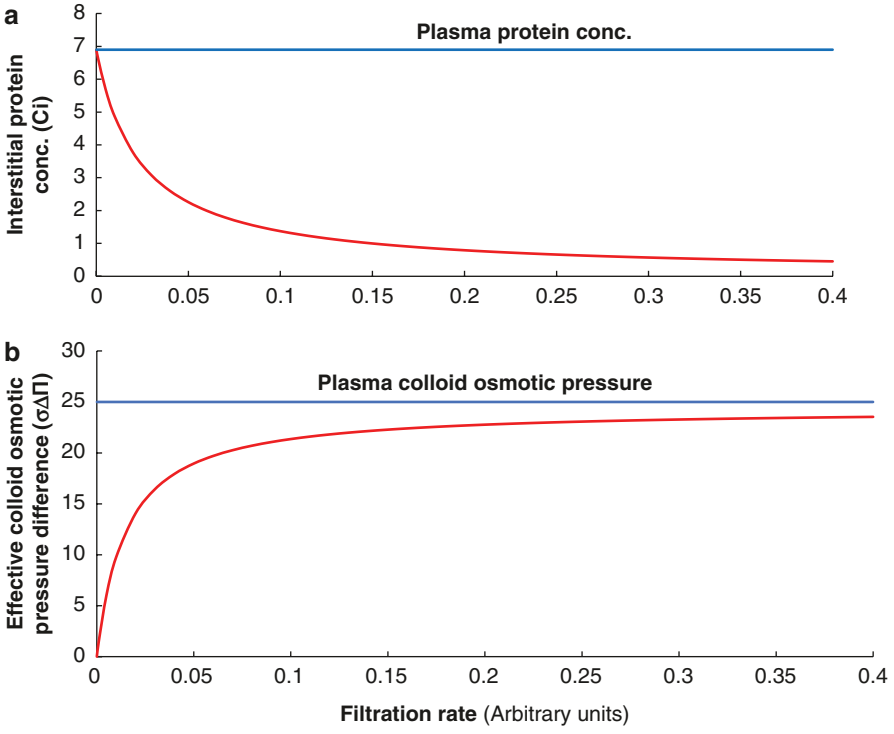

Fig. 2.6 The effects of changing filtration rate: (**a**) on steady state interstitial protein concentration and (**b**) the effective colloid osmotic pressure difference, $\sigma\Delta\Pi$, across microvascular walls. Note how $\sigma\Delta\Pi$ appears to reach a plateau at higher filtration rates

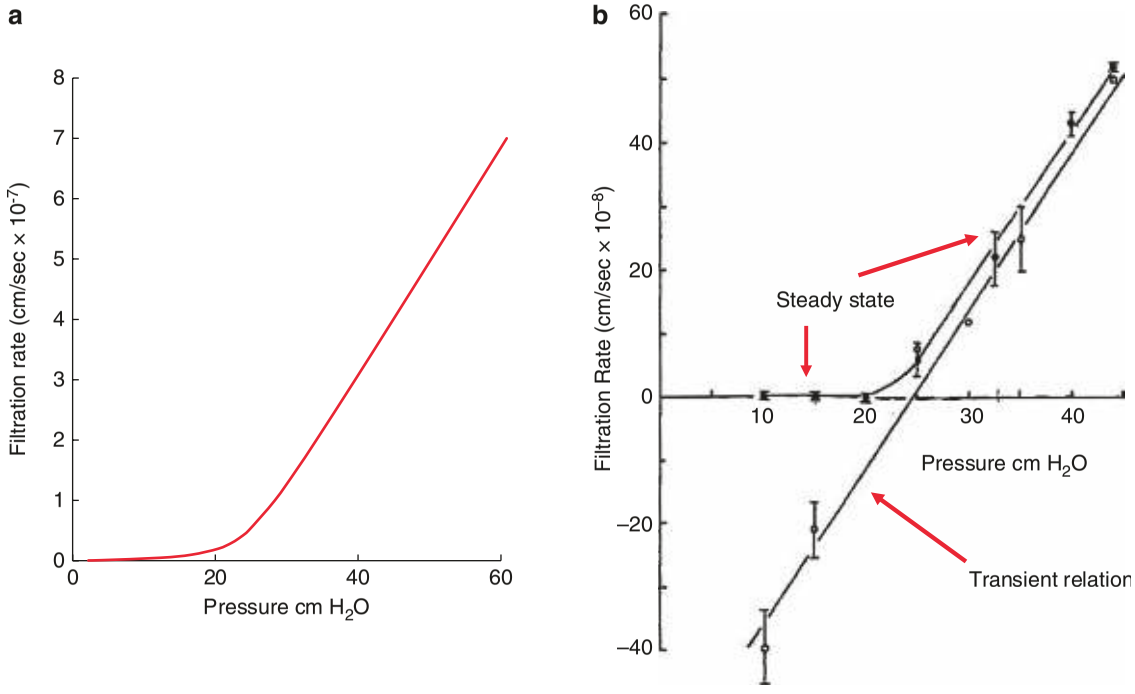

Fig. 2.7 (**a**) Steady state relations between fluid filtration rates and hydrostatic pressure difference across microvascular walls. At low pressures, steady state filtration increases only slightly with increments of pressure but as the pressure difference approaches the effective colloid osmotic pressure, filtration rate rises sharply and then increases linearly with pressure increments. This linear region develops as $\sigma\Delta\Pi$ becomes nearly constant in Fig. 2.6b. (**b**) The experiment on a single perfused mesenteric capillary demonstrating the transient and steady state relations between filtration rate per unit area of wall and capillary pressure. In this experiment the vessel was perfused initially at a high pressure (40 cm H_2O) and filtration rates measured at this pressure and then shortly after the pressure had been reduced as a step to a lower level. Steady values were then determined in the same vessel by measuring filtration rates after the vessel had been perfused at each pressure for 5–10 min. (Reprinted with permission from Michel CC, Phillips ME. Steady state fluid filtration at different capillary pressures in perfused frog mesenteric capillaries. J Physiol. 1987;388: 421–435.)

The curve was first published in a review as a way of interpreting measurements that had been reported in the literature and appeared inconsistent with contemporary interpretations of the Starling Principle in the early 1980s [32]. It departed in one conspicuous way from the traditional interpretation of Starling's Hypothesis (Fig. 2.2) in that it predicted there could be no steady state absorption of fluid into the microcirculation in tissues such as muscle, skin, and connective tissue where the interstitial fluid was formed entirely as an ultrafiltrate of the plasma. It was also inconsistent with the classical diagram for teaching Starling's Principle where there is a steady filtration from the arterial side of the microcirculation and a steady fluid uptake on the venous side.

Its general form was confirmed in experiments on single perfused microvessels, where most of the variables could be controlled with reasonable confidence (Fig. 2.7b) [37, 39]. The time course of the transient changes in fluid exchange following step changes in microvascular pressure to steady state values were also followed. The importance of making experimental investigations to check theory was underlined here, for while the experiments were able to confirm the shape of the steady state relation between fluid exchange and microvascular pressure and its relation to the transient changes, they also revealed that changes in fluid exchange from their initial values to their steady state values occurred far more quickly than was anticipated. This implied that the colloid osmotic pressure of the fluid immediately outside the exchange vessels reached their steady state values much more rapidly than the interstitial fluid as a whole. At the time it was thought that the relatively short time course of the transients was the result of slow equilibration of the proteins in the peri-vascular fluid with the rest of the interstitial fluids. Another possibility was that there were rapid changes in the interstitial hydrostatic pressure, but this seemed most unlikely in the exposed frog mesentery, which was continuously washed with a Ringer solution. Later experiments showed that in the exposed and superfused mesenteries of both frogs and rats, large changes in the filtration and absorption rates were accompanied by negligible changes in P_I when this was measured directly with a counter-pressure micropipette servo-nul system just outside the microvessels [39]. The experiment showing the change from the linear transient relation between fluid exchange and capillary pressure to the non-linear steady state relation is shown in Fig. 2.7b.

It is useful to consider that each point on the curved steady state relation between fluid exchange rate and ΔP is coincident with another linear relation that describes the transient increase in fluid exchange rate if pressure is raised or lowered. This is depicted in Fig. 2.8 where the solid curves represent the steady state relations and the parallel dashed lines are the transient relations. As mean hydrostatic pressure difference approaches and then exceeds the plasma colloid osmotic pressure, the steady state relation bends sharply upward and with further increases in ΔP the relation becomes linear and almost parallel to the transient relations. This is the stage, shown in Fig. 2.6a, b, where the concentration of plasma protein in the ultrafiltrate and the effective osmotic pressure difference across the vessel walls become nearly constant. In Fig. 2.8, we can trace how fluid exchange might change in a tissue when ΔP is suddenly reduced and remains low long enough for a new steady state to be established. Starting at point A on the steady state curve, the fall in pressure

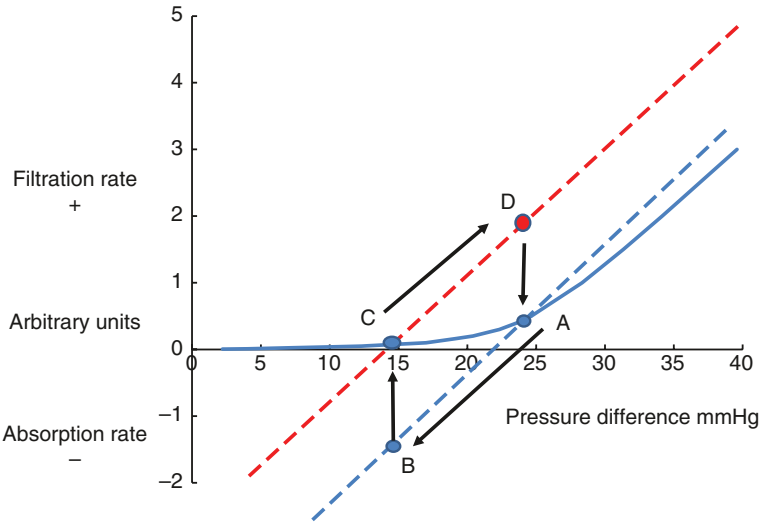

Fig. 2.8 Steady state relation between fluid movements and trans-capillary hydrostatic pressure difference (solid curve) and transient changes in fluid movement following step changes in hydrostatic pressure. Dashed lines represent transient relations (see text)

immediately moves fluid exchange from a low level of filtration to a brisk rate of fluid uptake from the tissues shown at point B. Then as a new steady state is established at the lower pressure, fluid absorption is reduced along the arrow at constant ΔP to point C where the steady state value of $\sigma\Delta\Pi$ consistent with this new level of ΔP is reached. If ΔP is now raised to its initial value, there is an immediate increase in filtration rate to point D, which is considerably greater than the initial steady state level, but this diminishes as the higher filtration rate increases $\sigma\Delta\Pi$ reducing filtration to the lower level at point A.

The rate at which a new steady state of fluid exchange is reached varies from tissue to tissue. In the pulmonary vascular bed, changes in fluid exchange rates following changes in mean capillary pressure attenuate to new steady state values within a minute or two. Here the changes in $\sigma\Delta\Pi$ are accompanied by changes in P_I, which become less sub-atmospheric (less negative) to buffer rises in P_C and more negative when P_C falls. In skeletal muscle, where initially P_C has been adjusted for fluid exchange between circulating blood and tissue to be undetectable, a subsequent step reduction in P_C is followed by brisk fluid uptake from the tissue which falls with time becoming undetectable after 30 min or more.

Steady State Fluid Uptake in Specialized Tissues

So far we have considered only those tissues where the interstitial fluid is formed entirely as an ultrafiltrate of the plasma flowing through its microcirculation and here we have concluded that there can be no continuous (steady state) fluid uptake

from interstitial space directly back into the blood. If edema is to be avoided in a tissue, the net gain of fluid by the interstitial space from microvascular filtration has to be balanced by drainage from the tissue of an equal volume of lymph. In tissues such as the cortex and medulla of the kidney and the intestinal mucosae, fluid is continuously absorbed into the microcirculation. In these absorptive tissues, the microcirculation lies close to epithelia, which secrete a protein-free solution into the interstitial fluid dominating its composition. It can be seen in Fig. 2.5 that these are the only tissues where the Starling pressures favor fluid uptake and in the case of the small intestine, this is true only during the absorptive phases. It seems that the protein-free secretion from the neighboring epithelium prevents the protein concentration from rising as fluid is absorbed into the circulation (see Fig. 2.9). The higher the rates of secretion of protein-free fluid into the ISF by the epithelium, the lower is Π_I, which increases $\sigma\Delta\Pi$ and so increases fluid uptake. In both the renal cortex and in the intestinal mucosa, lymph flow increases with absorption rates into the blood, preventing proteins from accumulating in the ISF so that steady uptake of fluid into the blood flowing through the microcirculation can continue. When the intestinal epithelium is no longer absorbing fluid and consequently not adding protein-free secretion to the ISF, fluid uptake into the microcirculation reverts to low levels of filtration (Fig. 2.5).

In the renal medulla, there are no lymphatics. Here interstitial proteins are carried directly back into the blood with the fluid that is absorbed into the ascending vasa recta. This process should concentrate the interstitial proteins, but this is

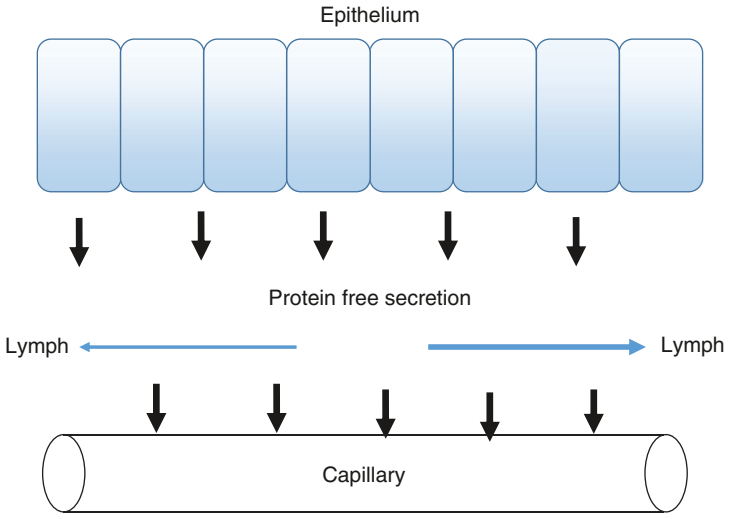

Fig. 2.9 Diagram to illustrate how the continuous uptake of fluid in capillaries of the intestine and renal cortex and medulla can be maintained by the secretion of protein-free fluid into the interstitial space from the nearby epithelium. In this way the protein concentration of the interstitial fluid can be prevented from rising and so maintains the effective colloid osmotic pressure difference across microvascular walls upon which fluid uptake depends

prevented by the continuous secretion of protein-free fluid by the epithelia of the collecting ducts and thick ascending limbs of the loops of Henle [40–42].

Steady fluid uptake also occurs into the high endothelial microvessels of lymph nodes [43]. Here the interstitial fluid is the lymph and its flow keeps protein concentration low enough for the effective osmotic pressure difference across the microvascular walls to be greater than the opposing hydrostatic pressure gradients ($\sigma\Delta\Pi > \Delta P$ in eq. 2.3).

Which Effective Colloid Osmotic Difference Is Relevant to Fluid Exchange?

Steady state fluid exchange helps us to understand why the neutral position for fluid exchange in tissues such as skeletal muscle is one of filtration. It does not, however, account for the high levels of net filtration, which may be calculated from eq. (2.4) using the plasma osmotic pressure and mean values of interstitial hydrostatic and colloid osmotic pressures in tissues such as muscle even when the venous pressure is substituted for the mean capillary pressure. Under transient conditions, the effective osmotic pressure that determines net fluid exchange is not the mean difference in pressures between the plasma and the interstitial fluid, but the hydrostatic and osmotic pressure differences across the ultra-filtering structures in microvascular walls. In experiments where the mean interstitial concentration of plasma proteins is maintained independently of the composition of the capillary ultra-filtrate, steady state differences can be maintained between the mean value of Π_I and the colloid osmotic pressure of ultrafiltrate emerging on the tissue side of endothelial ultrafilter [16]. Under physiological conditions, however, where the interstitial fluid of tissues such as skin and muscle is derived from the capillary filtrate, it is difficult to account for such large deviations (seen in Fig. 2.5) between the value of $\sigma\Delta\Pi$ across the microvascular filtering structures and that calculated from mean values for interstitial fluid and plasma under steady state conditions. The suggested solution to this question arises from the special characteristics of microvascular permeability to macromolecules.

It has been recognized for 60 years that most water and small water soluble molecules cross microvascular walls by a route that is not available to macromolecules. This pathway has been referred to as the "small pore pathway" because its permeability to water soluble molecules of differing molecular size can be modelled as diffusion and convection through a membrane penetrated by small cylindrical pores with radii of between 3.5 and 5 nm. The small pores have now been identified as the fluid-filled spaces between the fibrous molecules of the matrix that makes up the glycocalyx on the luminal surface of the endothelium. After crossing the glycocalyx of non-fenestrated endothelia, the ultrafiltrate flows through the intercellular clefts, being channeled through occasional breaks in the tight junctional strands to reach the basement membrane. To account for the permeability of microvascular walls to macromolecules, a second very much smaller population of larger pores has been proposed with radii of 15–30 nm. This is referred to as the "large pore pathway."

Box 2.3 Aquaporin Channels in Endothelia

There is an additional pathway for water molecules that involves the aquaporin channels of the endothelial cell membranes of continuous (non-fenestrated) endothelia. This has not been convincingly shown so far to account for more than 10% of the overall hydraulic permeability. Furthermore, since it is impermeable to small water soluble molecules and ions, the role of this pathway is unclear when net flows of fluid are driven by small hydrostatic pressure gradients.

There has been much controversy as to whether the "large pores" are indeed water-filled channels through which large and small molecules are carried by convection or whether their role is played by transcytosis. There are undoubtedly specific trans-endothelial transport mechanisms for some macromolecules in some vessels (e.g., transferrin in the cerebral capillaries) but the passage of many macromolecules (including the most plentiful plasma proteins) is increased by net filtration, consistent with convective transport, and follows a general pattern consistent with their molecular size and charge (Box 2.3).

Estimation of the colloid osmotic pressure difference across microvascular walls from the protein concentrations of the plasma and their mean values in the interstitial fluid assumes that there is complete mixing of the solutions leaving the small pores and the large pores on the tissue side of the endothelial cells. The effective osmotic pressure, however, is that exerted across the membrane components of the vessel wall that act as an ultra-filter; i.e., the glycocalyx. It was realized that if mixing of the solutions leaving the small and large pores could be prevented from occurring immediately behind the glycocalyx, the effective osmotic pressure difference across the vessel wall would be increased because a larger difference in protein concentration would be present across the pathway that had the higher osmotic reflection coefficient. Figure 2.10 shows how this difference should vary with the net fluid filtration rate. It should be noted that while the increase in $\sigma\Delta\Pi$ with the channels separated is only 4 mm Hg (an improvement of 20%) the important difference is that between the curves at higher filtration rates and the plasma colloid osmotic pressure is an improvement of 75%. The difference in effective osmotic pressure here approximates to plasma colloid osmotic pressure.

How can this separation of the downstream effluents from the two pathways be achieved? The deviations from a balance of the pressures revealed by Levick's analysis [34] showed that it was most significant in those microvessels where the endothelia were continuous (non-fenestrated). For these vessels the same possible mechanism for separating the flows was suggested independently by Michel [6] and Weinbaum [44]. Plasma ultrafiltrate, which is formed by flow through the glycocalyx at the luminal endothelial surface, has to pass by a tortuous route through infrequent breaks in the tight junctional strands of the intercellular clefts of the endothelium to reach its abluminal surface and the basement membrane (Fig. 2.11) [38]. The structural equivalent of the large pores are possibly very rare open intercellular clefts or channels formed by fused vesicles that pass directly through the endothelium to its abluminal surface. Macromolecules passing through these

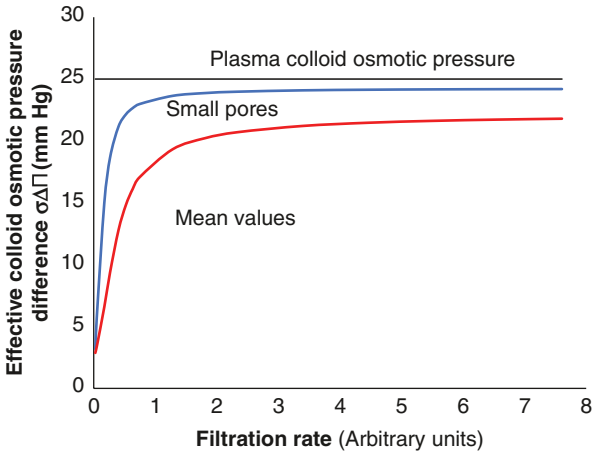

Fig. 2.10 Steady state relations between the effective osmotic pressure difference across skeletal muscle micro-vessels and fluid filtration rates comparing the mean values with those across the small pores (glycocalyx). Note how the effective osmotic pressure difference seen across the small pores (glycocalyx) approximates more closely to the plasma colloid osmotic pressure than the mean difference. The difference between $\sigma\Delta\Pi$ and Π_P across the small pores is a quarter of that based on mean values

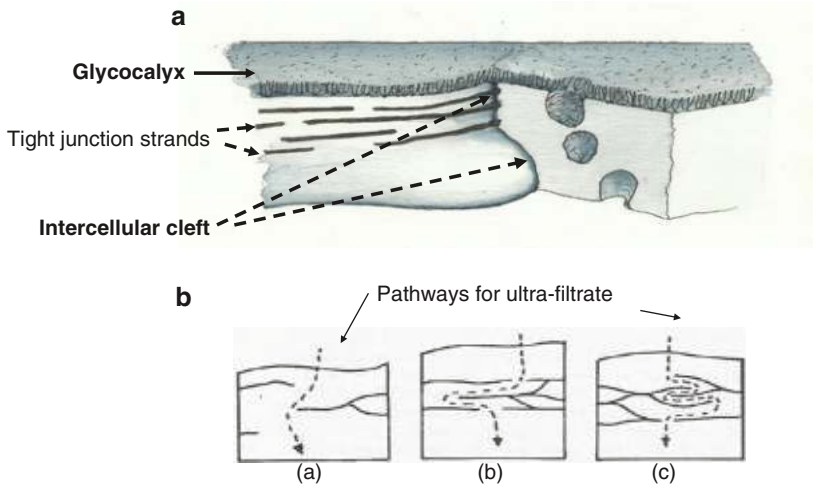

Fig. 2.11 Diagrams to illustrate the ultrastructure within an intercellular cleft between endothelial cells and the pathways through them for water and small hydrophilic solutes that have passed through the glycocalyx. (**a**) Part of the cell in the foreground has been removed to display the cleft interior. Note the junctional strands and the potential pathways through the breaks in them. (**b**) After flowing through the glycocalyx, which excludes macromolecules, the ultra-filtrate enters the luminal section of the intercellular cleft and is diverted to where there are breaks in the first tight junctional strand. The dashed lines with arrows indicate the potential pathways through intercellular clefts in different capillaries: (a) mesenteric capillary; (b) cardiac muscle capillary; (c) skeletal muscle capillary. (Reprinted with permission from Michel CC. Exchange of fluid and solutes across microvascular walls. In: Seldin DW, Giebisch G (eds). The Kidney: Physiology and pathophysiology. Vol 1. 2000. Philadelphia, Pennsylvania, USA: Lippincott, Williams &Wilkins. 2000: p 61–84)

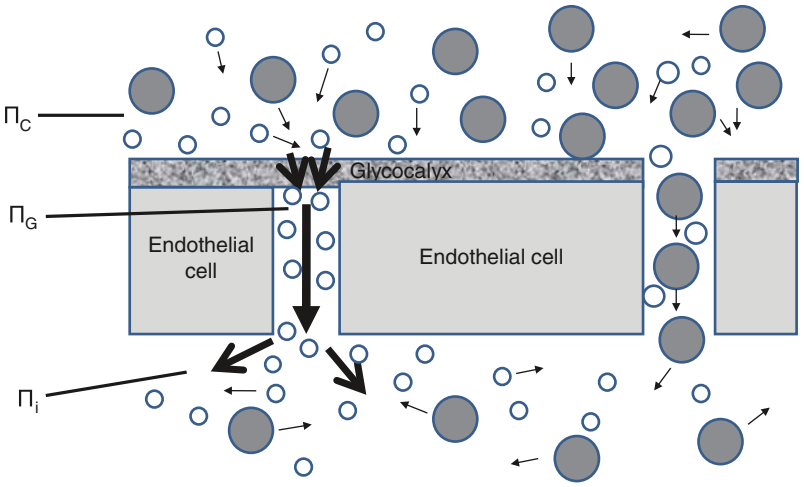

Fig. 2.12 A schematic diagram of fluid and protein exchange across walls of microvessels with continuous (non-fenestrated) endothelia. Small open circles represent water molecules; large filled circles represent protein molecules, with the plasma shown above the endothelium and the interstitial fluid below. Water crosses the endothelium through the intercellular clefts (left of picture) after having passed through the glycocalyx which filters out the protein (the small pores). Proteins cross by the large pore to the right of the picture below an opening in the glycocalyx. Large pores are relatively few (one per 10,000 small pores). The thickness and length of the arrows indicate the mean velocities of the molecules. Because the velocity of the water molecules in the intercellular clefts in amplified by 1–4 orders of magnitude, it prevents protein molecules from back diffusing up the clefts to the underside of the glycocalyx. (Reprinted with permission from Michel CC. Microvascular fluid filtration and lymph formation. In: Santambrogio L (ed). Immunology of the lymphatic system. New York: Springer, 2013: p 35–51)

channels from the plasma may be expected to arrive at the basement membrane and equilibrate with fluid there, most of which will have been filtered through the glycocalyx before passing through the intact intercellular clefts. In the absence of flow through the clefts, plasma proteins may be able to diffuse back through the breaks in the tight junctions to reach the underside of the glycocalyx. But calculations indicate that in the presence of even a low level of filtration through the intercellular clefts, such as might result from a difference in ΔP of as little as 1 cm H_2O, it is unlikely that proteins such as serum albumin would be able to back diffuse from the basement membrane beyond the tight junction. This is because the flow velocity of the filtrate as it leaves the underside of the glycocalyx is amplified many times over as it is funneled through the breaks in the junctional strands, which form the tight junctions. These openings constitute no more than 10% of the length of the clefts in the most permeable microvessels with continuous endothelium and in mammalian skeletal muscle, the freeze-fracture studies of the junctional strands suggest an open fraction of closer to 1%, which would increase the flow velocity of the fluid 100 times more than its velocity upon entering and leaving the intercellular clefts. Detailed modeling of this effect suggested that back diffusion of protein to the underside of the glycocalyx would be even less likely than initial rough calculations had indicated. The hypothesis is summarized in Fig. 2.12 [45].

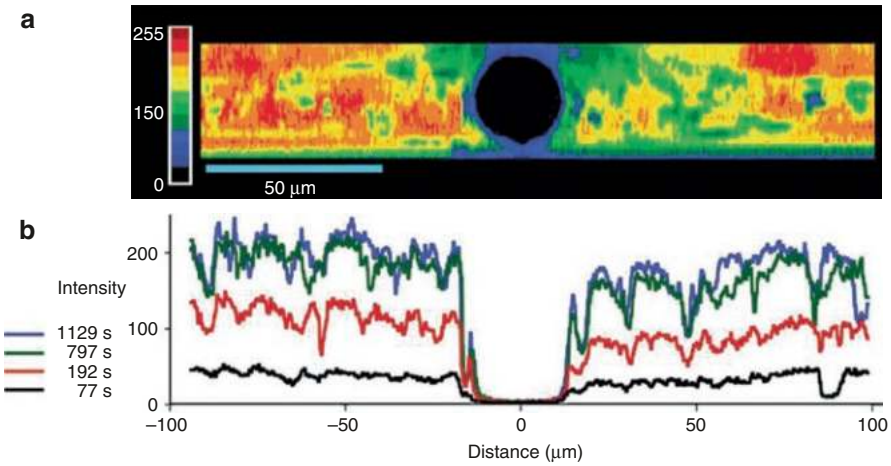

Fig. 2.13 Serum albumin concentration gradients around a venule in the rat mesentery at various times after fluorescently labeled albumin has been added to the superfusate. (**a**) Fluorescence image of a transverse section through the vessel and surrounding tissue. The vessel is perfused with an unlabeled albumin solution at the same concentration as the labeled albumin in the superfusate and appears as a dark circle. (**b**) Intensity profiles, taken from images such as that shown in (**a**), showing how the concentration in the tissue builds with time, taking between 12 and 20 min to a reach a steady state. It is seen that the interstitial albumin concentration in this experiment is equal to that in the superfusate within one μ(mu)m of the vessel lumen. (Reprinted with permission from Adamson RH, Lenz JF, Zhang X, Adamson GN, Weinbaum S, Curry FE. Oncotic pressures opposing filtration across non-fenestrated rat microvessels. J Physiol. 2004; 557: 889–907)

Shortly after this hypothesis was proposed, Curry suggested an experiment to test it. If the interstitial space is loaded with protein to the same concentration as that present in the plasma, it should only influence filtration rates through capillary walls when the microvascular pressures were below the plasma colloid osmotic pressure. This was soon shown to be so, first in single perfused capillaries of the frog mesentery [46] and later in rat mesenteric venules [47]. Figures 2.13 and 2.14 are taken from the paper by Adamson et al. [47]. In each experiment, a single microvessel was perfused *in situ* through a micropipette with a Ringer solution containing 5% serum albumin while the exposed surface of the mesentery was washed initially with a protein-free Ringer solution (the superfusate). The relations between fluid filtration rates and microvascular pressures were determined for the vessel and the effective osmotic pressure exerted by the perfusate opposing filtration was determined.

The superfusate was then changed to one that was identical to the perfusate in all respects except here the albumin was fluorescently labelled so its presence in the tissues could be monitored. When the fluorescent intensity of albumin surrounding the perfused capillary had reached the level indicating that its concentration was equal to that inside the vessel, the relations between the fluid filtration rates and microvascular pressure was re-determined. Under these conditions, one might

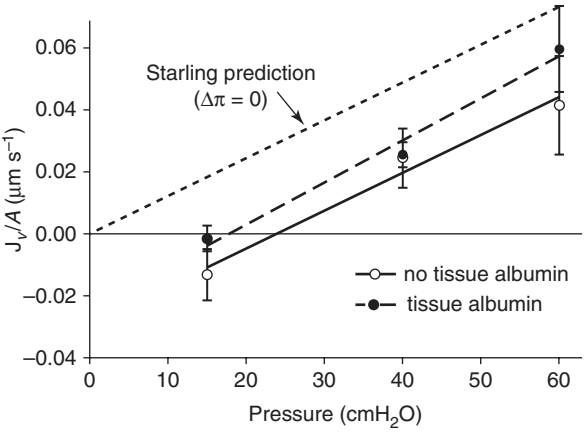

Fig. 2.14 Transient relations between filtration rates from a rat venule and microvascular pressure perfused with a solution containing serum albumin (50 mg/ml) when the superfusate washing the surface of the mesentery contains no albumin (open circles) and the same albumin concentration as that in the solution perfusing the vessel (closed circles). Measurements of filtration rates were made when there appeared to be no difference in albumin concentration across the vessel walls. The classical interpretation of Starling's principle would predict the relation should pass through the origin of the graph. The large intercept at $J_V/A = 0$ indicates a substantial colloid osmotic pressure still opposes filtration. (Reprinted with permission from Adamson RH, Lenz JF, Zhang X, Adamson GN, Weinbaum S, Curry FE. Oncotic pressures opposing filtration across non-fenestrated rat microvessels. J Physiol. 2004; 557: 889–907)

expect that the effective osmotic pressure opposing filtration from the vessel would now be zero. Where, however, pressure was several cm H_2O above the colloid osmotic pressure of the perfusate, the effective osmotic pressure opposing filtration was very little less than it had been when the superfusate contained no protein. Furthermore, as shown in Fig. 2.14, the transient changes in filtration rate when microvascular pressure was dropped to lower levels remained unchanged. Only when the vessel was perfused at low levels for a few minutes did the effective osmotic pressure opposing filtration diminish. The experiments clearly demonstrate how the effective osmotic pressure difference across microvascular walls may be independent of the mean colloid osmotic pressure of the interstitial fluid. Furthermore, the changes in filtration rates with pressure are entirely consistent with the prediction of the Michel-Weinbaum hypothesis, strengthening its claim as an explanation of low filtration rates consistent with local lymph flows.

This series of experiments also confirmed the validity of the steady state theory and like the earlier experiments of Michel and Phillips [37] found that the transition from transient to steady state fluid exchange occurred very much more quickly than would be expected if it involved the entire interstitial fluid of the tissue equilibrating with microvascular filtrate. Electron microscopy of mesenteric microvessels reveals that these vessels are closely sleeved by pericytes. It was argued that the narrow spaces between the abluminal surface of the endothelial cells and the

pericytes act as a compartment or "micro-domain," which equilibrates quickly with the capillary filtrate, rapidly increasing the rate at which a new steady state is established [48].

A Picture to Forget

A popular textbook diagram to illustrate the Starling Hypothesis depicts a linear fall in pressure along a capillary with its value at the arterial end in the range of 35 mm Hg and with the venous end around 15 mm Hg (Fig. 2.15a). This sloping line crosses the horizontal line, which indicates the colloid osmotic pressure of the plasma of 25 mm Hg. In the space between the lines when pressure is greater than 25 mm Hg, a series of downward pointing arrows indicate fluid being filtered from the vessel into the tissues; over the second half of the capillary when pressure is less than 25 mm Hg, the arrows point upward, indicating the uptake of fluid from the

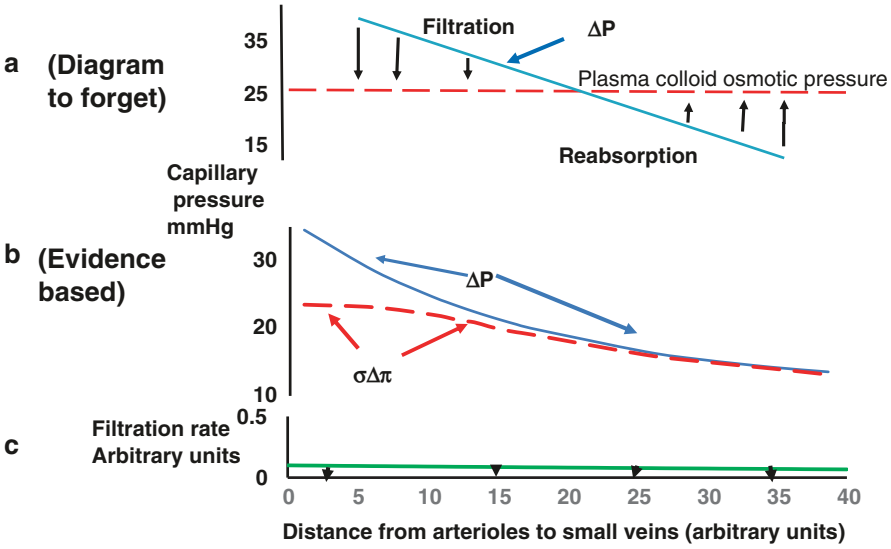

Fig. 2.15 (**a**) Version of the widely used textbook diagram to illustrate Starling's Hypothesis with filtration occurring in the upstream section of an exchange vessel where $\Delta P >$ plasma colloid osmotic pressure, Π_p, and absorption downstream where $\Delta P < \Pi_p$. Interstitial colloid osmotic pressure is incorporated by subtracting its mean value from Π_p at all points along the vessel. (**b**) Changing values of ΔP and $\sigma\Delta\Pi$ across the microcirculation of a tissue such as skeletal muscle under steady state conditions consistent with revised Starling Principle. $\Delta P > \sigma\Delta\Pi$ at all points although difference is less than 1 mm Hg for a majority of vessels. If net filtration were indicated by arrows drawn between the curves for ΔP and $\sigma\Delta\Pi$ as in (**a**), its low near constant value across the microcirculation would not be conveyed. (**c**) When differences in exchange surface area and L_P are taken into account, near constant filtration into the tissues consistent with $\Delta P - \sigma\Delta\Pi$ is achieved as expected

tissues. This diagram has been remarkably successful in enabling medical students to satisfy their examiners with their understanding of blood-tissue fluid exchange. Attractive though it is, the diagram implies several things for which there is no experimental evidence and are probably never true.

The diagram suggests that it represents the net fluid movements in a typical microcirculation such as that of skin or muscle. Quite apart from there being no evidence that both filtration and absorption occur simultaneously in these microcirculations (see later), it would be atypical of most vascular beds for it implies that the exchange vessels are present in equal numbers at the arterial and venous ends of a microcirculation and are also of equal permeability to fluid and macromolecules. Arterioles, arteriolar capillaries, mid-capillaries, and venules are all recognized to be involved in the blood-tissue exchange of solutes. In the arterioles, exchange is probably confined to the respiratory gases with fluid exchange occurring to some degree in all the other exchange vessels downstream. There are more mid-capillaries than arterial capillaries resulting in an increase in the surface area of the vessel walls available for exchange. The exchange area is further increased by an increase in vessel radius as one moves to the venular capillaries. In most tissues, the wall surface area is maintained in the small venules where a reduction in the number of vessels is compensated for by an increase in vessel diameter. There are two obvious consequences. First, the fall in hydrostatic pressure is greatest between arterioles and mid-capillaries and becomes progressively less steep as one passes through the microvascular bed toward the veins; this has been demonstrated very clearly in microcirculations of mesentery and skeletal muscle [49]. Second, the increase in area available for exchange means that even if the hydraulic permeability were the same in all exchange vessels, a small difference in pressure across vessel walls at the venous end of the microcirculation has greater net effect on fluid exchange than it would have at the arterial end. Also, where measurements of L_P have been made in single vessels, L_P has higher values in venular capillaries and venules than in vessels upstream. If this arterio-venous gradient of L_P is present in most microvascular beds, it will multiply with the increasing area for exchange and be consistent with the conclusion reached earlier: that microvascular fluid exchange occurs mainly in the region of the venular capillaries and venules.

An obvious criticism of Fig. 2.15a is that it ignores, Π_I, the colloid osmotic pressure of the interstitial fluid. We have seen that Π_I cannot be taken as a constant that can be subtracted from the plasma colloid osmotic pressure. For the revised Starling Principle, the colloid osmotic pressure difference, which influences fluid exchange, is that across the glycocalyx. This varies with the filtration rate and ultimately with the hydrostatic pressure difference across the vessel wall. As we have seen, the colloid osmotic pressure underneath the glycocalyx can differ considerably from the mean colloid osmotic pressure of the ISF. To illustrate this for a microcirculation such as that in skeletal muscle, the hydrostatic pressure difference, ΔP, and the effective colloid osmotic pressure difference, $\sigma\Delta\Pi$, have been plotted against the distance from the arteriolar capillaries to the larger venules in Fig. 2.15b. The nonlinear fall in ΔP is shown as the upper curve and the lower curve is $\sigma\Delta\Pi$, estimated for steady state conditions of fluid exchange. Whereas the difference $(\Delta P - \sigma\Delta\Pi)$ is

initially more than 10 mm Hg, it is soon reduced to 1 mm Hg and continues to fall to less than this. The largest differences in pressure driving fluid from plasma to tissue are seen in the arteriolar capillaries, which contribute least to the exchange area of the microvascular bed. Probably they also have the lowest values of L_P and so the net movement of fluid from blood to tissue from this part of the microcirculation is relatively small. This is illustrated in Fig. 2.15c, which shows a low and almost constant level of fluid filtration from the plasma as it flows through the microvascular bed.

The low level of filtration represents the steady state condition in microcirculations of tissues such as muscle. These low levels of filtration are expected in muscle tissues when subjects are supine and P_C lies in the range of 15–35 mm Hg, but most of the daytime of healthy subjects is spent standing, sitting, and walking when most of their body lies below heart level and when P_C is both variable and considerably higher than this range [13, 14, 32]. These conditions do increase interstitial volume in the lower parts of the body and increase the lymph flow from them [50]. Some of this additional extravascular fluid will be absorbed directly into microcirculation during the first hour of bed rest, but probably more is absorbed from the lymph as it flows through the lymph nodes. Independent studies by Adair et al. [43] and Knox and Pflug [51] demonstrated that the protein concentration of post-nodal lymph was on average twice that in pre-nodal lymph. Both groups investigated lymph flows through the popliteal nodes of anesthetized dogs. Estimates of the pre-nodal and post-nodal lymph flows by Adair et al. [43] indicated that the doubling of protein concentration in the post-nodal lymph was accompanied by a halving of lymph flow, indicating that half the pre-nodal flow was absorbed into the blood flowing through the node. Knox and Pflug [51] noted that the ratio of concentrations in the post-nodal lymph to those in the pre-nodal lymph was the same for all proteins and independent of their absolute values. From this they concluded that higher concentrations in the post-nodal lymph were consistent with fluid removal from the lymph as it flowed through the node rather than by the addition of protein to the lymph. Further experiments in which labelled albumin was injected directly into the pre-nodal lymph confirmed this interpretation [51]. Because lymph flows through the nodes and continually renews the fluid outside the blood capillaries and venules, steady state fluid uptake can occur here. Its importance can be appreciated if we make rough estimates of the volume of fluid filtered daily from plasma into the total muscle mass of a human subject.

Skeletal muscle mass of a 70 kg male subject is approximately 28 kg and estimates of the product of L_PA for soft tissues of the forearm and calf regions, which are largely muscle, lie in the range of 0.0025 to 0.004 ml min^{-1} mm Hg^{-1} 100 g^{-1} of tissue. Using the difference $(\Delta P - \sigma\Delta\Pi)$, as shown in Fig. 2.15b, and averaging it over the exchange area of the muscle microcirculation leads to a mean value of just less than 1 mm Hg. Using these values, one calculates a net daily filtration of between 800 ml and 1300 ml. These figures represent the basal levels that might occur during sleep (or bed rest) and additional volumes of fluid filtered into muscles of the lower half of the body during sitting or standing would probably double these figures. If during the first hour or so of bed rest transient absorption of fluid was

driven by a mean pressure of 2 mm Hg, 100–300 ml of extravascular fluid might be absorbed directly into the circulation. A further 800–1300 ml would be absorbed from the lymph flowing through regional lymph nodes over 8 h of bed rest and possibly a similar volume during the daytime. This would mean that of the 1600–2600 ml of fluid filtered into skeletal muscle during a day, between 900 ml and 1600 ml would be absorbed mostly at the lymph nodes leaving a remaining volume to be added to thoracic duct lymph of between 700 ml and 1 L. The estimates of the thoracic duct lymph flow in human subjects have been restricted to a few measurements made on patients with thoracic duct fistulae and are approximately 4 L per day in non-fasting subjects when two-thirds of the lymph is derived from the liver and gastrointestinal tract. Since skeletal muscle constitutes 40% of the total body mass, a contribution of approximately 20% to thoracic duct lymph seems reasonable. This is a rather more realistic figure than that to which Levick [34] drew attention 29 years ago. Following the argument implied in Fig. 2.15a, by subtracting mean ISF Π_I from Π_P, Bates et al. [52] found that ($\Delta P - \sigma\Delta\Pi$) exceeded the **venous** pressure in human forearm skeletal muscle by 4–5 mm Hg. Because the mean capillary pressure is likely to be 5–15 mm Hg greater than the venous pressure, the net pressure driving filtration throughout the microvascular bed could be as high as 10 mm Hg. Even if it were only 5 mm Hg and also that both the patient remained supine and half the fluid filtered into 28 kg muscle were absorbed in the lymph nodes, there would remain 6 L of fluid to be added to thoracic duct lymph every day; i.e., 150% of the maximum estimates for the sum of the daily flows for both thoracic duct and right lymph ducts. However useful Fig. 2.15a may have been as an *aide mémoire*, it is misleading and cannot be used for clinical decision making. Figure 2.15b is much closer to the truth.

Relevance of the Revised Starling Principle to Intravenous Fluid Therapy

Woodcock and Woodcock [4] drew attention to the relevance of the revised Starling Principle in guiding and interpreting the effects of intravenous fluid therapy. The name "Revised Starling Principle" is, however, unfortunate for it implies that the original principle was incorrect and required revising. Perhaps because of this misnomer, the revised Starling Principle has been misunderstood and subsequently misrepresented.

For example, in a recent publication [53] it is said that the revised Principle "has challenged the traditional Starling formula equation", that "the plasma's oncotic pressure is less important than previously thought" and that fluid absorption from the tissues does not occur. It has also been suggested that the "Revised Principle" predicts that the movement of fluid from the interstitial spaces into plasma can only occur via the lymphatics and not by raising the plasma colloid osmotic pressure [53]. All these statements are incorrect.

First, far from challenging the equation which describes the classical Starling Principle, the development uses the traditional equation to show what its

consequences are when the exchange vessels in tissues have a low but finite permeability to macromolecules.

Second, the revised principle does ***not*** say that fluid uptake from the tissues cannot occur. If this were so, it would be difficult to account for fluid uptake from the gastro-intestinal tract or reabsorption of most of the glomerular filtrate in the kidneys, let alone the inconsistency between such a claim and the large body of evidence demonstrating the direct uptake of fluid from the tissues into the blood, including Starling's own experiments. What the revised principle does say is that where the ISF of a tissue is formed entirely from the ultrafiltrate of the plasma flowing through its microcirculation, fluid uptake from tissues directly into blood is always transient. Thus, a fall in the mean microvascular pressure difference across microvascular walls below the effective colloid osmotic pressure difference between plasma and ISF in these tissues results in fluid uptake from ISF directly into the circulating plasma but the rate of fluid uptake diminishes with time and eventually reverts to a low level of filtration. The revised principle argues that in these tissues, steady states of blood-tissue fluid exchange are established only when there is at least a very low level of net filtration of plasma into tissues. This is an obvious conclusion since in this type of tissue where all the ISF is generated by filtration from the plasma. The volume of the ISF here is maintained by a low level of filtration into the tissue, which is matched by the flow of lymph out of the tissue. These tissues include both skeletal and smooth muscle, skin and connective tissues and constitute a large fraction of the body mass. In tissues where the source of some ISF is a protein free secretion from adjacent epithelia (eg in the intestinal mucosa and the post glomerular renal microcirculation) steady state conditions of fluid uptake can occur (as discussed in section on "Steady state fluid uptake in specialized tissues").

Third, following on from this, the revised Starling Principle does **not** suggest that raising the colloid osmotic pressure of plasma is an unimportant method for moving fluid from ISF into plasma. This, of course, increases the effective colloid osmotic pressure difference across microvascular walls and if this difference now exceeds the difference in hydrostatic pressures, fluid should flow from tissues into circulating blood.

Perhaps the most important contribution that the Revised Principle might make to peri-operative care lies not so much in the detail of the steady state relations or even the recognition that there often are differences between the mean colloid osmotic pressure of the ISF and that of the peri-capillary fluid but by the graphical analysis used to demonstrate that fluid exchange is determined by $\boldsymbol{\Delta P - \sigma \Delta \Pi}$ as Starling recognized. When this difference is positive, fluid is filtered from the circulation into the tissues. When the difference is negative, fluid is absorbed into the plasma from the tissues. The rates of filtration and absorption are directly proportional to these differences and serve to return fluid exchange to the point on the steady state curve at that value of ΔP. While ΔP in the different tissues cannot be measured, their presence cannot be neglected when trying to interpret changes following intravenous infusions. To illustrate this, we consider a question central to the controversy of whether intravenous infusion of crystalloid solutions is more effective in expanding plasma volume of patients with severe blood loss than it appears to be in normovolemic subjects.

Consider first a healthy volunteer in a supine resting position, in whom Π_P has an initial value of 25 mm Hg and the mean value of P_C is 23 mm Hg. If a purely crystalloid solution is intravenously infused in this subject, it dilutes the plasma protein, decreasing Π_P, and increasing $\Delta P - \sigma\Delta\Pi$ and consequently increasing filtration from plasma to tissues. The filtration rate increases further if P_C rises as the blood volume expands, either as a consequence of an increase in cardiac output or of a compensatory vasodilatation (with a reduction of the pre- to post capillary resistance ratio) particularly in skeletal muscle, with its large contribution to the total body mass. Glomerular filtration rate and subsequently urine flow both increase, resulting in the slow excretion of the fluid load. A large number of studies of this kind have been carried out, notably by Hahn and his colleagues and analyzed using their volume kinetics model [54–56].

Anecdotal reports that crystalloid infusions are more effective than this in clinical situations has been supported in a series of trials, which have found that for patients in intensive care, similar hemodynamic measures can be achieved by volumes of crystalloid solutions only slightly greater than those of solutions containing colloids (e.g. [57, 58]). A mechanism for the increased effectiveness of crystalloid infusions under these conditions involves the physiological response to hypovolemia. Hypovolemia triggers vasoconstriction in much of systemic circulation and the consequent increase in precapillary resistance (particularly in skin and muscle) greatly increases the Ra/Rv ratio and lowers P_C (see eq. 2.2 above). The fall in P_C may be increased further by an accompanying fall in P_a with a reduced cardiac output. Such a fall in P_C results in the driving pressure for filtration, $\Delta P - \sigma\Delta\Pi$, becoming negative and consequently fluid moves from ISF into the plasma. These changes are shown in terms of the relations between filtration and absorption rates and P_C in Fig. 2.16a and b. In Fig. 2.16a, the expected changes in filtration rate and P_C are shown following intravenous infusion of crystalloid solution in the healthy normovolemic subject. The vertical arrow, AB, indicates the rise in filtration rate if ΔP remains constant and the line, AC, how this rise may be amplified if, as seems likely, ΔP increases. The changes in the hypovolemic patient are shown in Fig. 2.16b. Here, the effects of the instantaneous vasoconstriction are the same shown as for a step fall in ΔP, previously illustrated in Fig. 2.8. If the vasoconstriction and consequent fall in ΔP occurs more slowly, a curvilinear path might be followed. The upward pointing vertical arrow indicates the effects of either the physiological uptake of fluid from the tissues or infusing a crystalloid solution at constant P_C. Intravenous infusion of crystalloid solutions at this stage not only speeds up this process of restoring the circulating volume but aids its completion. Reports in the older literature indicate that physiological compensation is limited in the short term. Kaufmann and Müller [59] reported that in healthy individuals, estimates of the dilution of the plasma proteins immediately after blood donations of 400 ml, indicated that while 50–60% of the plasma volume was restored in 15 min, no further changes occurred over the subsequent 15 min. The effects of both physiological compensatory fluid uptake and intravenous crystalloid infusions should be the same, diluting the circulating plasma protein concentration and consequently shifting the position of the steady state curve so that its inflexion occurs at a lower value of

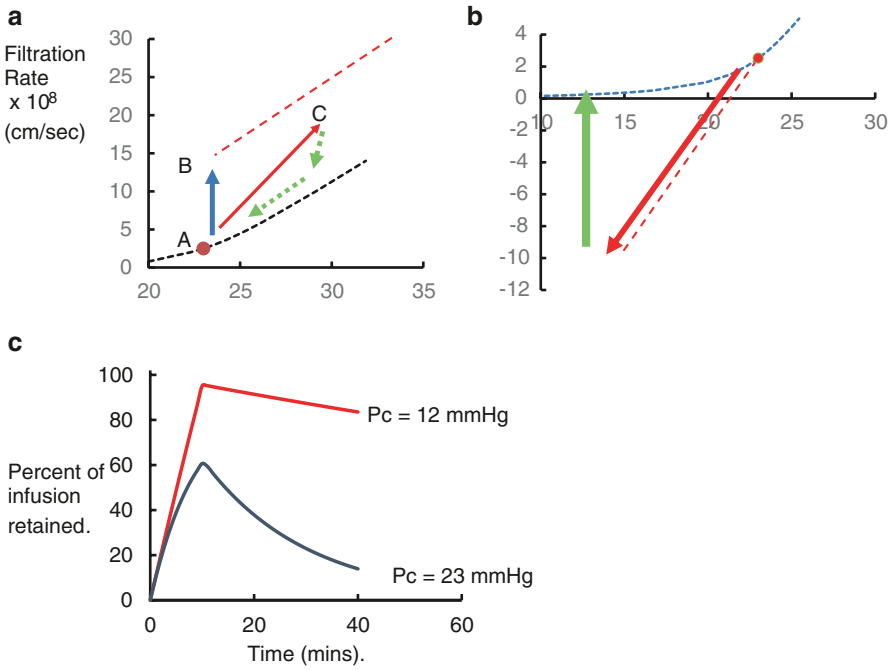

Fig. 2.16 Relationships between microvascular fluid filtration (J_V/A) and microvascular pressure difference (ΔP) before during and following intravenous infusion of an isotonic crystalloid solution. Point A indicates values of J_V and ΔP before infusion and blue arrow, the changes in J_V/A at constant ΔP to point B where infusion ends. If, as is most likely, expansion of the circulating volume leads to vasodilatation, with reduced *Ra/Rv* and a consequent rising P_C, changes in J_V are shown by the red arrow leading towards point C. Green dashed arrows indicate excretion of the fluid load. (**b**) Changes in *Jv/A* in an acutely hypovolemic patient. Initial vasoconstriction with increase in *Ra/Rv,* leads to a rapid fall in Pc with a consequent reversal of fluid filtration to fluid uptake from tissues to plasma (red arrow A to B). If crystalloid solution is infused at B, fluid is retained and plasma volume restored to a degree determined by dilution of plasma proteins to the stage where $\sigma\Delta\Pi = \Delta P$ at the value of *Pc* at point C. Fluid is no longer retained if infusion is continued beyond this stage (**c**) Predictions of the fraction of a crystalloid infusion that is retained in the circulation in a tissue such as muscle at normal and reduced P_C

ΔP. Based on the calculations underlying Fig. 2.16a, b, and assuming the mean value of the product of the hydraulic permeability and exchange surface area for all the microvascular beds of the body is similar to that in human skeletal muscle, the percentage of the infusion which is retained in the circulation over a 40 min period are shown for the healthy subject and the patient in Fig. 2.16c. We have pointed out that in the hypovolemic patient, the infusion of crystalloid solutions has the same effect on Π_P as the physiological compensatory response of absorption of largely protein-free fluid from tissues into the plasma. One big difference, however, is that as Π_P is reduced and $\sigma\Delta\Pi$ falls towards ΔP in the vasoconstricted systemic circulation, the rate of physiological fluid uptake into the plasma also decreases and comes

to halt when $\sigma\Delta\Pi = \Delta P$. Unfortunately, the clinician has no obvious means of knowing when this occurs. In most organs and tissues supplied by the systemic circulation, a low level of edema is reversible but this is not the case for the pulmonary circulation. The greatest risk from over-transfusion is pulmonary edema.

The clinician may, however, be guided by the revised interpretation when considering the effects of fluid therapy on the pulmonary circulation. The lungs of healthy individuals are protected from edema by the low microvascular pressures in pulmonary capillaries (7–10 mm Hg) and by the speed with which transient changes in filtration rate reach new steady state values following small changes in the Starling pressures. In addition to the brisk increase of $\sigma\Delta\Pi$ that follows an increase in filtration rate, there is also a reduction of ΔP since interstitial hydrostatic pressure in the lungs lies normally in the range of −5 to –10 mm Hg (sub-atmospheric) and rises rapidly with expansion of pulmonary interstitial volume acting as an additional buffer against edema formation. The low pulmonary capillary pressures mean that fluid filtration rates sit on the flat region of the steady state curve, 10 mm Hg or more below its upward inflection (similar to point C in Fig. 2.16b). This means that dilution of the plasma proteins during intravenous infusions of crystalloid solutions should have little effect upon pulmonary interstitial volume until the plasma colloid osmotic pressure is reduced to a value just above the mean pulmonary P_C. When large fluid volumes are infused intravenously, a logical precautionary measure might be to monitor patients' plasma protein concentrations, or even better, their plasma colloid osmotic pressures together with pulmonary artery pressure. The infusion of crystalloid could then be discontinued as soon as the colloid osmotic pressure approached 10–12 mm Hg.

Although changes in circulating plasma volume are shown in Fig. 2.16c, it should be remembered that the near constant value maintained for nearly 30 min following a 12 min infusion of crystalloid solution when P_C = 12 mm Hg is predicted on the assumption that P_C remains low and all micro-vessels have the same permeability properties to fluid and macromolecules as those found in skeletal muscle of healthy subjects. This, of course, is, at best, an approximation. Until there is a more complete quantitative understanding of the dynamics of blood volume regulation and methods available for assessing this in the operating room, predictions of the effects of intravenous infusions are at best imprecise. At present, there is no easy way for the clinician to know the value of the mean P_C in most major components of the systemic circulation.

A Note on the Measurements of Changes in Plasma Volume

To manage intravenous fluid therapy efficiently one should have a rapid and reliable method for estimating changes in plasma volume. Unfortunately, there is no method of this kind available. Whereas plasma volume can be estimated from the dilution of a labeled plasma protein, the time taken for the tracer to mix sufficiently to reach a uniform concentration within circulation is sufficient for a significant fraction of tracer to have left the plasma and entered the tissues. To remedy this, serial

measurements of plasma tracer concentration are made and once they are seen to follow a steady exponential decline, back-extrapolation to zero time (the time of injection) provides a value of concentration that can be taken to represent that which would be present when the injected mass of tracer was uniformly distributed throughout the plasma volume. Hence if m is the amount of tracer injected into the circulation, C_0 is the concentration at zero time and V_P is the plasma volume, then $V_P = m/C_0$. This is not a method that can be used to estimate rapidly changing plasma volumes and most investigators have instead used changes of hematocrit as an index of the relative changes in plasma volume when total red cell volume in the circulation is considered to be constant. This may seem to be a reasonable approach but it involves major uncertainties. Before considering these, let us revise the basic idea of the method. Let H be the hematocrit and V_C and V_P are the total circulating volumes of the red cells and plasma, it seems reasonable to say:

$$\frac{H}{100} = \frac{V_C}{V_C + V_P}, \text{and}$$

$$\frac{100}{H} = \frac{V_C + V_P}{V_C} = 1 + \frac{V_P}{V_C} \tag{2.6}$$

Let H_1 be the hematocrit of a sample of blood taken from a patient before a procedure and H_2 be its value 40 min after infusion of 500 ml of a crystalloid solution. Providing the total volume of circulating red cells has remained unchanged, the ratio of the plasma volumes corresponding to H_1 and H_2 is calculated from eq. (2.6) as:

$$\frac{\frac{100}{H_2} - 1}{\frac{100}{H_1} - 1} = \frac{V_{P2}}{V_C} \cdot \frac{V_C}{V_{P1}} = \frac{V_{P2}}{V_{P1}} \tag{2.7}$$

The relative change in plasma volume is:

$$\frac{V_{P2} - V_{P1}}{V_{P1}} = \frac{V_{P2}}{V_{P1}} - 1 = \frac{(100/H_2) - 1}{(100/H_1) - 1} - 1 \tag{2.8}$$

If, initially, the total volumes of circulating plasma and cells are 3 L and 2 L respectively and 300 ml of the infused 500 ml of crystalloid solution is retained when the blood has a hematocrit of H_2, then V_{P2}/V_{P1} should equal 1.1, and plasma volume would be 3.3 liters. If H_1 was 40% then H_2 should be 37.7%. With an error of 1% in the estimation of hematocrit, H_1 could be 41% and H_2 = 37%. Using these slightly erroneous values, the relative change in plasma volume would be estimated as 1.183. With an initial plasma volume of 3 L, the measured change of hematocrit would now suggest the plasma volume was 3.550 L, an overestimate of 250 ml and a plasma volume 50 ml greater than the infused volume. This calculation emphasizes how very small errors in the measurement of hematocrit lead to large errors in

the interpretation of changes in plasma volume. Obviously, such errors can be minimized by making multiple determinations of hematocrit on each blood sample.

A second problem, when estimating changes of plasma volume from changes in hematocrit, arises from the differences between the hematocrit determined on blood taken from a large vessel and that calculated from measurements of the total plasma volume and total red cell volume, the whole body hematocrit. In most individuals the large vessel hematocrit (H_{LV}) is greater than the whole body hematocrit (H_M), with the ratio of H_M/H_{LV} (described as the F-cell ratio) falling between 0.88 and 0.94 for most healthy (and non-pregnant) adults [60–63]. In pregnancy (where maternal blood volume is expanded) the ratio falls and in the new born it may be as low as 0.8 [60]. Variations in the ratio in the same individual occur from time to time and it is suggested that these are associated with the redistribution of blood in the systemic circulation [64]. Thus estimates of changes of plasma volume with acute changes in posture using dye dilution have been reported to be twice as great as those made from changes in hematocrit [64].

A contributing factor is that red cells circulate through most peripheral circulations more rapidly than plasma and that rather than representing the ratio of the volume of red cells to the volume of blood, the hematocrit in large vessels reflects the ratio of the flow of cells to the flow of blood. The flows of red cells and plasma are related to their overall volumes through their mean transit times. If τ_c and τ_p are transit times for the red cells and the plasma respectively, then eq. (2.6) may be rewritten as:

$$\frac{100}{H_{LV}} = 1 + \frac{V_P}{V_C}\frac{\tau_C}{\tau_P} \tag{2.9}$$

When a change of plasma volume is calculated from eq. (2.7), the result becomes:

$$\frac{\left[\left(100/H_1\right)-1\right]}{\left[\left(100/H_2\right)-1\right]} - 1 = \frac{V_{P2}}{V_{P1}} \cdot \frac{\tau_{C2}}{\tau_{C1}} \cdot \frac{\tau_{P1}}{\tau_{P2}} - 1 \tag{2.10}$$

where subscripts 1 and 2 represent the initial and final volumes and transit times respectively. Only if the ratio τ_c/τ_p remains unchanged will the estimate of a change in V_p be correct. A small change in the value of τ_c/τ_p accompanying a change in V_P can lead to misinterpretation.

This can be illustrated by the following numerical example. If the intravenous infusion of a fluid increases V_P from 3.0 to 3.5 l and is accompanied by an increase in red cell velocity relative to plasma velocity, reducing τ_c/τ_p from 0.9 to 0.85, by ignoring the transit time ratios one might conclude that the increase in plasma volume was 306 ml instead of 500 ml; i.e., an underestimate of just under 40%. If, by contrast, the red cell velocity was slowed by the infusion, increasing τ_c/τ_p from 0.9 to 0.95, ignoring this change would suggest that the increase in plasma volume was 694 ml—an overestimate of nearly 40%. This margin of error indicates that small changes in the relative transit times of red cells and plasma in the circulation can compromise estimates of changes in plasma volume following the intravenous infusion of fluids. The message from this is that estimates of changes in plasma volume

based on changes in large vessel hematocrit should be regarded with critical caution [64].

Conclusion

The so-called "revised Starling Principle" develops the interpretation of Starling's Hypothesis in two ways. First it recognizes that the permeability of microvascular walls to macromolecules means that there is never an equilibrium between the hydrostatic and colloid osmotic pressure between the plasma and interstitial fluid. The colloid osmotic pressure difference is itself dependent on filtration of fluid from plasma into the tissues, and fluid uptake from ISF to plasma can only occur transiently in tissues where the ISF is formed entirely as a plasma filtrate. Steady state uptake of fluid into the circulation occurs only in those tissues where a large component of the ISF is a protein-free secretion from a neighboring epithelium or where the ISF flows through the tissue as in lymph nodes.

The second way in which the revised principle develops the classical hypothesis is that it recognizes that the difference in colloid osmotic pressure holding fluid within the vascular system is not between that of the plasma and its mean value for ISF but the difference across the primary ultra-filtering structure within microvascular walls. This is the glycocalyx at the luminal surface of endothelium. In vessels with continuous (non-fenestrated) endothelia, the low flux of macromolecules, which cross the endothelium by breaches in the glycocalyx, are prevented from back-diffusing from the basement membrane to the underside of the glycocalyx by a low level of filtration, the velocity of which is amplified a hundredfold during its passage through the narrow breaks in the junctional strands. As a consequence, the relevant effective osmotic pressure across the glycocalyx differs from the difference in colloid osmotic pressure between that of the plasma and its mean value for the interstitial fluid.

When plasma colloid osmotic pressure, Π_P, is constant, changes in net fluid transport rates are transiently directly proportional to step changes in hydrostatic pressures. With different time courses in different tissues, these initial rates move toward steady state values. Graphs relating steady state fluid transport to microvascular pressures in most tissues (e.g., muscle, skin, connective tissues) are not linear, showing a marked inflection when microvascular pressures are close to plasma colloid osmotic pressure. As pressure rises between 0 and Π_P, fluid filtration is very small and difficult to detect; when pressure is greater than Π_P, filtration rate rises sharply, and with further increases in pressure becomes linear with a slope equal to the hydraulic permeability of the microvascular wall. This nonlinear behavior of steady state fluid exchange is of potential importance in guiding intravenous fluid therapy. It predicts that the effects of dilution of the plasma proteins and reduction of Π_P on blood-tissue fluid exchange are different when microvascular pressure (P_C) is in the range of Π_P and when P_C is well below this. When P_C is initially equal to or greater than Π_P, dilution of the plasma increases filtration into tissues; when P_C is well below Π_P, dilution of the plasma proteins has little effect. This is because

the steady state filtration rates at normal and reduced Π_P differ by very little until Π_P falls to within a couple of mm Hg of the low P_C. Low values of P_C occur in muscle with intense peripheral vasoconstriction (e.g., following blood loss) and are also normally present in pulmonary capillaries. This suggests that monitoring Π_P may help to avert pulmonary edema during infusions of large volumes of crystalloids.

Appendix

Some readers may be interested to follow the theoretical derivation of the steady state relation between fluid filtration through a membrane and the pressure difference across the membrane when the solute responsible for an osmotic pressure difference opposing filtration has a reflection coefficient of less than one.

The rate of transport of the solute through the membrane is J_S and transport occurs by convection (fluid filtration per unit area of membrane = J_V) and diffusion (diffusion coefficient of the solute in the membrane water = D). If the overall thickness of the membrane between its upstream and downstream surfaces = Δ and x = any distance measured in the membrane from the upstream surface between 0 and Δ, the flux of solute at x is given by:

$$J_S = J_V\left(1-\sigma\right)C(x) + D\left(-\frac{dC(x)}{dx}\right),$$

Where C(x) is solute concentration at x. Rearranging this expression leads to:

$$\frac{dC\left(x\right)}{dx} = \frac{J_v\left(1-\sigma\right)}{D}\mathrm{C}\left(\mathrm{x}\right) - \frac{J_S}{D}. \tag{2.11}$$

Both J_S and J_V are time invariant in the steady state and σ and D are constants; defining $a = J_V(1-\sigma)/D$ and $b = J_S/D$, allows simplification of 2.1A to:

$$\frac{dC\left(x\right)}{dx} = a.C\left(x\right) - b. \tag{2.12}$$

When x = 0, $C(x) = C_1$ the concentration of solute as the solution enters the membrane; when x = X, $C(x) = C_2$, the concentration solute in the ultrafiltrate leaving the membrane. Integrating eq. (2.12) between the limits of 0 and X:

$$\int_0^X \frac{dC\left(x\right)}{\left(aC\left(x\right)-b\right)} = \int_0^X dx \,\text{leads to}:$$

$$\ln\frac{\left(aC_2-b\right)}{\left(aC_1-b\right)} = aX, \,\text{which may be written as}:$$

$$\mathrm{a}C_2 - b = \left(aC_1 - b\right)e^{aX}. \tag{2.13}$$

The exponent, aX, is the ratio of the convective velocity of the solute through the membrane to its diffusion velocity and is known as the Péclet number, Pe. In the steady state, the ratio $J_S/J_V = C_2$, and dividing eq. (2.13) through by a and expressing the full meaning of a and b leads to:

$$C_2 = C_1 e^{Pe} - \frac{b}{a}\left(e^{Pe} - 1\right) = C_1 e^{Pe} - C_2 \frac{\left(e^{Pe} - 1\right)}{\left(1 - \sigma\right)},$$

Which can be reduced to:

$$\frac{C_1}{C_2} = \frac{\left(e^{Pe} - \sigma\right)}{\left(1 - \sigma\right)e^{Pe}}. \tag{2.14}$$

Dividing the RHS of 2.4 through by e^{Pe} and inverting yield

$$\frac{C_2}{C_1} = \frac{\left(1 - \sigma\right)}{\left(1 - \sigma e^{-Pe}\right)} \tag{2.15}$$

The concentration difference across the membrane is:

$$C_1 - C_2 = C_1 \sigma \frac{\left(1 - e^{-Pe}\right)}{\left(1 - \sigma e^{-Pe}\right)} \tag{2.16}$$

If we assume the osmotic pressures of the solutions at the upstream surface and leaving the membrane downstream are directly proportional to their solute concentrations, the difference in osmotic pressure opposing filtration, $\Delta\Pi$, can be expressed in terms of the upstream osmotic pressure, Π_1,

$$\Delta\Pi = \Pi_1 \sigma \frac{\left(1 - e^{-Pe}\right)}{\left(1 - \sigma e^{-Pe}\right)} \tag{2.17}$$

For fluid filtration through microvascular walls, Π_1 is equivalent to Π_P, the plasma colloid osmotic pressure, so that the steady state relation between fluid filtration and microvascular pressure difference can be written (approximately) as:

$$J_V = L_P \left[\Delta P - \sigma^2 \Pi_P \frac{\left(1 - e^{-Pe}\right)}{\left(1 - \sigma e^{-Pe}\right)}\right]. \tag{2.18}$$

Equation (2.19) resembles eqs. (2.1) and (2.3) but because Pe is a function of J_V the equation should be written as an expression for ΔP in terms of J_V.

$$\Delta P = \frac{J_V}{L_P} + \sigma^2 \Pi_P \frac{\left(1 - e^{-Pe}\right)}{\left(1 - \sigma e^{-Pe}\right)} \tag{2.19}$$

When appropriate values for the permeability coefficients are substituted into eq. (2.19), non-linear curves similar to those shown in Figs. 2.6, 2.7 and 2.14a can be

constructed. Equations (2.18) and (2.19) are approximations because the assumption made in eq. 2.17 is only approximately true as the relation between osmotic pressure and concentration for macromolecular solutions is not linear but its slope increases with concentration and it is best described by a polynomial expression. To obtain more accurate predictions, numerical solutions can be used to estimate the osmotic pressure difference from the difference in concentration.

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3 The Functions of Endothelial Glycocalyx and Their Effects on Patient Outcomes During the Perioperative Period: A Review of Current Methods to Evaluate Structure-Function Relations in the Glycocalyx in Both Basic Research and Clinical Settings

Fitz Roy E. Curry, Kenton P. Arkill, and C. Charles Michel

Abstract

The endothelial glycocalyx establishes the osmotic pressure difference of the plasma proteins across the vascular wall and plays a major role to determine the distribution of infused fluids in both normal and clinical settings. Loss of the glycocalyx compromises the retention of infused fluid in the plasma volume. On the basis of results from improved approaches to preserve and image glycocalyx structures, and quantitative evaluations of water and red cell interactions with glycocalyx components, the glycocalyx is now best understood as fibrous networks with varying composition within a three dimensional structure: a quasi-periodic inner matrix associated with the endothelial cell membrane that forms the permeability barrier, and a more porous outer region whose composition varies with distance from the endothelial membrane and which determines red cell hemodynamics. This chapter evaluates the strength and weakness of experimental and theoretical investigations that have led to this understanding and points to

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the emerging methods to investigate glycocalyx structure using advanced imaging methods. The increasing awareness of the importance of changes in the glycocalyx as an early indicator of microvascular dysfunction in both acute and chronic disease requires methods to evaluate the glycocalyx in the clinical setting. The methods to measure whole body glycocalyx volume from the difference between the distribution volumes of red cells and macromolecular tracers overestimate glycocalyx volume and are likely of limited usefulness. The common concept that the changes in the thickness of the glycocalyx layers extending more than 0.5 μm from the endothelial surface can be used as reliable biomarkers of the function of the glycocalyx as a permeability barrier must also be carefully evaluated. While direct visualization of changes in the penetration of red cells into the cell-free layer at the walls of sublingual microvessels appears to characterize some glycocalyx dysfunction, the approach ignores differences in porosity between inner and outer layers of the glycocalyx, and the role of changes in red cell mechanics, independent of the glycocalyx, to influence penetration into the cell free layer. By identifying these limitations, the chapter should provide a basis to re-evaluate ideas about the distribution of infused fluids within and across the glycocalyx during perioperative fluid therapy, encourage further improvements of these and similar methods, and enable comparisons with analytical approaches to measure the accumulation of specific glycocalyx components in plasma and urine as biomarkers of glycocalyx function. On the basis of the principles outlined in this Chapter, the final summary addresses some of the frequently asked questions about glycocalyx function and fluid balance that are likely to arise during perioperative fluid therapy.

Key Points

1. The glycocalyx establishes the osmotic pressure difference of the plasma proteins across the vascular wall and plays a major role to determine the distribution of infused fluids in both normal and clinical settings. One of the most important modern concepts in perioperative fluid therapy is that loss of glycocalyx components is an early step in microvascular dysfunction, leading to disturbances of plasma volume and transvascular fluid distribution.
2. The glycocalyx is extremely difficult to preserve and visualize in its normal state. The glycocalyx is best understood as a fibrous network with varying composition within a three-dimensional structure. A quasi-periodic inner matrix associated with the endothelial cell membrane forms the permeability barrier and a more porous outer layer determines red cell hemodynamics. The common concept that the changes in the thickness of the glycocalyx layers extending more than 0.5 microns from the endothelial surface can be used as biomarkers of glycocalyx function in model systems and patients must be carefully evaluated.
3. Preservation of the glycocalyx requires suppression of matrix metalloproteinase activity and free radical generation and avoidance of conditions of both hypovolemia and hypervolemia. The potent glycolipid antiinflammatory agent

sphingosine-1-phosphate (S1P) plays a critical role to maintain glycocalyx and endothelial barrier integrity. S1P is carried in the circulation by albumin and the Apolipoprotein-M fraction of high density lipoprotein. Conditions that limit S1P availability (low Apo-M levels and decreased synthesis of S1P) likely contribute to loss of endothelial glycocalyx.

4. The most direct evidence of damage to the glycocalyx comes from increased concentrations of glycocalyx components in the circulation or urine. New analytical methods based on mass spectroscopy may measure organ specific changes in glycocalyx injury. Measurements of a glycocalyx volume as a difference between the distribution volumes of red cells and macromolecular tracers such as dextran and albumin always overestimate the volume of plasma within the glycocalyx and are not a reliable index of the way the glycocalyx modifies intravascular fluid distribution.
5. Direct visualization of changes in the penetration of red cells into the cell free layer at the walls of sublingual microvessels of patients using side stream dark field imaging is currently being actively evaluated as a biomarker of changes in the glycocalyx. While there is increased penetration of red cells towards the vessel wall in microvessels vessels up to 50 μm in diameter in some disease states, the claim that such changes are a reliable biomarker of the function of the glycocalyx requires much more careful evaluation, particularly with regard to changes in the glycocalyx that are important for peri-operative fluid therapy.

Introduction

Glycocalyx is a term that describes the sugar based extracellular matrix present on all cells. The endothelial glycocalyx is a specialized version and forms the first contact surface between blood and tissue. It is involved in physiological responses that determine tissue homeostasis including fluid, nutrient, and large molecule transport between blood and tissue. Preclinical investigations have demonstrated that the glycocalyx forms part of the barrier that regulates water and large molecules movement through vascular endothelium, senses the magnitude of local blood flow and regulates local nitric oxide production. The glycocalyx also senses the direction of local blood flow and modulates endothelial remodeling, and forms the layer over which red cells transit through microvessels. By limiting access of leukocytes and other vascular cells, including platelets, to the endothelial surface, the glycocalyx also plays a key role in inflammation and the coagulation system [1–8]. These homeostatic functions are compromised when all or part of the glycocalyx is lost or damaged [9–12]. Mounting evidence also indicates that a clear understanding of the functions of the glycocalyx has the potential for improved clinical outcomes in both acute and chronic disease states including interventions involving perioperative fluid management [13–15]. The glycocalyx is the primary determinant of fluid flows and plasma protein concentration differences between circulating blood and the body tissue, and the consequences of this for fluid therapies is described in accompanying Chap. 2 on the Revised Starling Principle.

In this Chapter the focus is on the evolving understanding of the glycocalyx as a 3-dimensional layered structure close to the endothelial surface. Figure 3.1 shows a state-of-the art view of the glycocalyx on a glomerular capillary built up from images obtained by the process of focused ion beam scanning electron microscopy in which layers of fixed tissue 10 nm thick are successively removed [16]. The image is from the most recent of a series of investigations reported by the authors of this chapter that have provided new understanding of structure-function relations in the glycocalyx in both fenestrated and non-fenestrated microvessels fixed under a variety of conditions and using both conventional as well as newer ways to stain glycocalyx components ([16, 17] and see Sections "Imaging the Glycocalyx and Structure-Function Relationships" and "Background: Imaging the Glycocalyx: More Detailed Technical Issues" below). An evaluation of such a 3D structure is important because: (1) the regulation of the different physiological functions of the glycocalyx described above (e.g. permeability barrier versus lubrication layer for

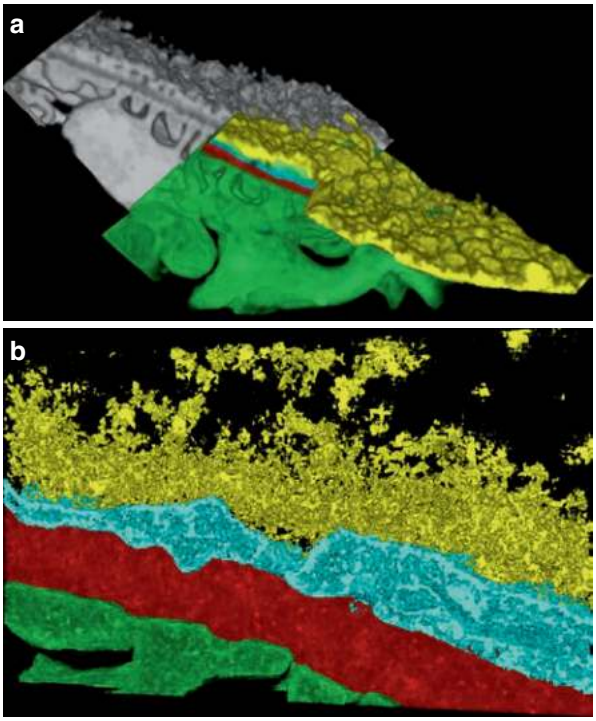


Fig. 3.1 The endothelial glycocalyx of a renal glomerular filtration capillary. The original data (from [16] with permission) was: (**a**) 3D series built from a scanning electron microscope sequence with 10 nm of material milled away between images by a focused ion beam. The front edge of glycocalyx is 4 μm wide. (**b**) 3D reconstruction of a transmission electron tomogram into a 1.2 μm by 0.73 μm by 0.16 μm cuboid. The glycocalyx was stained with the LaDy GAGa technique. The figure with parts of the glycocalyx (yellow), endothelium (blue) and podocyte foot processes (red) colored for emphasis is adapted from [16]. Details of the glycocalyx staining and 3D scanning electron microscopy of the glycocalyx are in Sect. 10

red cell movement through microvessels) depends of different properties of its substructure; (2) measurements of biomarkers for glycocalyx function in clinical settings (distribution space for red cells in microvessels or the volume of the glycocalyx) can result in misleading estimates of changes in the glycocalyx structure when its 3D organization is not taken into account; (3) understanding the mechanisms that degrade the glycocalyx or that contribute to its protection and stability require knowledge of the heterogeneity of the glycocalyx and its internal organization; and (4) new approaches to the investigation of the glycocalyx at a molecular level require better understanding of the limitations of current approaches which often assume that the glycocalyx is a relatively uniform structure.

We discuss these topics below, beginning with a brief overview of glycocalyx composition in relation to 3D structure, and how current knowledge provides some insight into ways to protect the glycocalyx. In the second part of the review we evaluate approaches to measurement of changes in the glycocalyx both in clinical settings and in basic research. Because of the layered structure we generally use the term glycocalyx to describe the molecular components that form a physical structure directly and indirectly attached to the endothelial cell surface. The term endothelial surface layer (ESL) is also often used as a less specific term to describe the region next to the blood vessel wall, and is generally assumed to also refer to the whole glycocalyx but it is likely that the thickness of the ESL is modulated by mechanisms in addition to the glycocalyx, including the micromechanics of red cell movement through blood vessels.

Composition in Relation to a Layered Structure

Overall the glycocalyx is a complex fibrous network of molecules that extends from the endothelial cell membrane for distances that range from about 0.5 to possibly several microns. The mechanisms determining the overall organization of the glycocalyx are still poorly understood but include the anchoring of core proteins to the endothelial cell membrane and its underlying cytoskeleton, charge interactions between the side chains of these core proteins, which carry a net negative charge, and other electrostatic and weak chemical interactions with plasma constituents including hyaluronan, plasma proteins, and small electrolytes. The structure is maintained by a dynamic balance between mechanisms to degrade the layer and mechanisms for its restoration by synthesis of components. This is suggested by the top panel of Fig. 3.2. There are several detailed reviews of glycocalyx structure [2, 4, 5, 8]. Here we briefly review the properties of known components that can be used to place constraints of glycocalyx structure. As illustrated in the lower panel of Fig. 3.2, these include:

(a) The syndecan family of core proteins: Endothelial cells (ECs) express several forms of this family which have glycosaminoglycan (GAG) attachment sites close to their N-terminus substituted by heparan sulfate (HS) [19]. Syndecan-1 contains two additional sites closer to the membrane for chondroitin sulfate

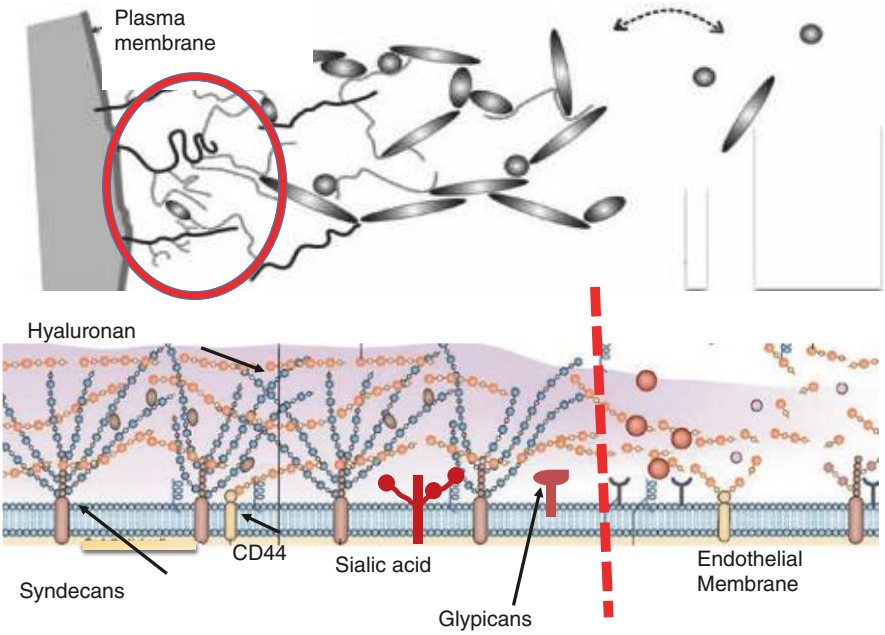


Fig. 3.2 One of the earliest attempts to illustrate the endothelial glycocalyx as a complex three-dimensional structure is shown in the top panel. The hypothetical model emphasizes the presence of an inner region consisting of glycoproteins and proteoglycans associated with the endothelial cell membrane and an outer layer with structure and composition varying with distance from the endothelial surface and in the plane of the endothelial surface. Hyalunonan forms part of the scaffold for the outer layer, which also includes adsorbed plasma proteins and solubilized glycosaminoglycans. A more detailed recent illustration of some of the inner structure components is shown in the lower panel. The physical and chemical properties of components of the inner layer have guided recent attempts to quantify the functions of glycocalyx as a permeability barrier and to form part of the lubrication layer for red cells. The section to the right of the red dashed line shows the consequence of glycocalyx degradation resulting in exposure of endothelial cell surface receptors to circulating plasma components. Top panel from [3] with permission. Lower panel modified from [18] with permission

(CS) [20]. Syndecans have many biochemical roles and often dimerize with cytoplasmic tails associated with the cytoskeleton. These attachments are assumed to play a role in the organization of the glycocalyx and contribute to signal transduction mechanisms [21–25]. Because the molecular weights of GAGs and core proteins suggest molecular lengths from the endothelial surface of the order of 100 nm, i.e. ~0.4 nm per disaccharide residue and >200 residues, it is likely that syndecans form part of the inner layers of the glycocalyx [26].

(b) The glypicans: Glypican-1(64 kDa), a member of the Glypican family of core proteins, is expressed on ECs. Glypican-1 is bound directly to the plasma membrane through a C-terminal glycosylphosphatidylinositol (GPI) anchor [27]. The GPI anchor localizes this proteoglycan to specialized membrane microdo-

mains, often termed lipid rafts, that include the endothelial surface caveolae. The GAG attachment sites in Glypican-1 are exclusively substituted with heparan sulfate.

(c) Hyaluronan: In contrast to these core proteins, hyaluronan or hyaluronic acid (HA) is a much longer disaccharide polymer, of the order of 1000–10,000 kDa (lengths can be of the order of several microns), synthesized on the cell surface and not covalently attached to a core protein [23]. HA associates with the glycocalyx through its interaction with surface receptors, such as the transmembrane glycoprotein CD44, and CS chains [28–30]. Because of its large molecular dimension and cable forming property, HA side chains can extend well beyond the core proteins and thereby form part of the scaffold for the glycocalyx [31, 32]. HA is not sulfated but obtains its negative fixed charge density from carboxyl groups that endow it with exceptional hydration properties.

(d) Plasma Components: The interaction of many plasma proteins with the endothelial surface is regulated by charge and chemical binding with the side chains of the glycosaminoglycans (see for example [33]). Of particular importance to the organization of the glycocalyx is albumin, which not only binds to the glycocalyx via positively charged arginine and lysine groups to contribute to stability and organization, but also is part of a signaling cascade that regulates matrix metalloproteinase release to degrade the glycocalyx (see details in Section "Restoration and Preservation of the Glycocalyx").

(e) Loss of Glycocalyx components: One of the most important modern concepts in vascular physiology is that loss of glycocalyx components is an early step in vascular dysfunction [6, 9, 34]. Similarly, loss of glycocalyx components indicates that the integrity of the endothelial barrier as an osmotic and permeability barrier has been compromised. The most direct evidence of damage to the glycocalyx comes from increased concentrations of glycocalyx components in the circulation or urine, above that due to the normal breakdown and continual reconstitution of the glycocalyx at the vascular interface. Examples of conditions that have been associated with glycocalyx damage include hypovolemia, leading to poor tissue perfusion and subsequent ischemia/reperfusion-injury [35], diabetes [36], sepsis [37–39], and exposure to a range of inflammatory agents including tumor necrosis factor-(α), cytokines, proteases, heparinase, and viruses such as the Dengue virus [40, 41]. Most current analytical techniques to measure circulating glycocalyx components rely mainly on ELISA based assays, which, though of varying specificity, do provide clear evidence of loss of glycocalyx components after injury. Examples include increased syndecan-1 (42-fold from a baseline of 12 ng/ml) and heparan sulphate (ten-fold from a baseline of 5 mg/ml) in patients undergoing major vascular surgery [42] and increased syndecan-1 (27.1–110 ng/ml) and HA (16.8–35.0 ng/ml) in dialysis patients [43]. Similarly increased levels of plasma HA in type 1 diabetes are associated with increased circulating level of hyaluronidase (170–236 U/ml). All these methods require extensive and relatively slow analytic procedures. This limitation is a major driver of attempts to develop more direct approaches to evaluate the glycocalyx as will be discuss later. Nevertheless it is likely that

detailed analyses of the chemical composition of glycosaminoglycan products and core proteins in circulating plasma using sophisticated mass spectroscopy and other spectrographic methods will become an important part of future analyses. This is especially the case if the origin of fragments from different vascular locations can be identified. For example, using these more sophisticated methods a 23 fold increases in the amount of HS fragments after lung injury has been reported [44].

Restoration and Preservation of the Glycocalyx

The glycocalyx is a dynamic structure whose structure and function is determined by the balance between synthesis and degradation of glycocalyx components [9, 11, 45]. In both animal models and clinical studies, direct restoration of glycocalyx components to circulating plasma (e.g. HA and CS [29]) or the infusion of glycosaminoglycan precursors, are reported to restore some function [46]. However the mechanisms to stimulate synthesis and reassembly of the glycocalyx remain to be investigated in much more detail.

Useful insight into the balance between stabilization of the glycocalyx and its degradation came from the observation that albumin, previously understood as an essential structural component of the glycocalyx, was part of a homeostatic mechanism that regulates glycocalyx degradation. Specifically, Zeng and colleagues [47] demonstrated that heparan sulphate, chondroitin sulphate, and the ectodomain of syndecan-1 were shed from the endothelial cell surface after removal of plasma proteins, but were retained in the presence of the potent glycolipid antiinflammatory agent sphingosine-1-phosphate (S1P) at concentrations greater than 100 nM. S1P1 receptor antagonism abolished this protection of the glycocalyx by S1P and plasma proteins. The action of S1P to preserve glycocalyx components was shown to involve suppression of matrix metalloproteinase (MMP) activity by S1P. Specific inhibition of MMP-9 and MMP-13 also protected against glycocalyx loss [47]. These results are consistent with observation in other animal experiments that activated MMPs lead to loss of glycocalyx and increased leukocyte attachment. Further, agents such as doxycycline that protect the glycocalyx act, at least in part, by inhibiting MMPs [48].

Another key observation was that, after red cells were removed from the perfusate, albumin alone was not sufficient to maintain the normal permeability of rat mesenteric microvessels. However when both albumin and red cells were present, or when albumin solutions were pre-conditioned by exposure to red cells, permeability was maintained and S1P concentrations in the perfusate exceeded 100 nM [49]. These observations established that albumin not only binds S1P but also facilitates the release of S1P from red cells and carries it to the endothelium. Normally albumin carries 40% of the circulating S1P [50].

The actions of S1P and abumin-bound-S1P to regulate glycocalyx degradation are now recognized as part of a wider range of actions of S1P to stabilize the endothelial barrier. Previous investigations demonstrated that S1P and S1P analogs

maintained the barrier by stabilizing adhesion complexes between adjacent endothelial cells, focal adhesion to extracellular matrix, and the actin cytoskeleton [45]. Equally important is the growing understanding of the delivery of S1P to the endothelial surface receptors by Apolipoprotein-M, a component of high-density lipoproteins (HDLs), which binds S1P and carries up to 60% of the circulating S1P [50, 51]. The Apo-M fraction of HDLs likely contributes to the vasoprotective actions of HDLs. Both albumin bound S1P and Apo-M bound S1P modulate the stability of intercellular junction complexes, but investigations by Hla and coworkers demonstrate that there is preferential activation of S1P receptors and signaling pathways in endothelial cells depending on the carrier [50, 52]. For Apo-M this may involve co-operative interaction of S1P and HDL binding sites on the endothelium and glycocalyx. In in vitro investigations, Apo-M delivery is more effective than albumin delivery to modify junctional complexes but the actions of Apo-M dependent delivery to stabilize the glycocalyx and to modulate release of S1P from circulating sources have not been investigated. A recent report also describes a separate pathway for S1P to protect the glycocalyx and junction complexes via mechanisms to inhibit mitochondrial dysfunction [53].

Some of the SIP-dependent mechanisms regulating the glycocalyx are illustrated in Fig. 3.3. The clinical significance of these new areas of investigation is that S1P delivery may be limited in a number of disease states. For example, reduced plasma Apo-M levels have been associated with acute myocardial infarction, endotoxemia, diabetes, and metabolic syndrome [52]. It is possible that the capacity to carry S1P may also be limited by oxidation of HDL or albumin glycosylation. Further, although it is known that activated platelets secrete S1P, the primary source of S1P in normal plasma is red cells that synthesize and store high levels of SIP [54]. There may be reduced synthesis of S1P in diseased or infected red cells. Also the increased mortality and morbidity described in patients transfused with red cells older than about I4 days may be explained, in part, by reduced S1P synthesis and corresponding loss of glycocalyx protection [54].

Other strategies to protect the glycocalyx involving inhibition of proteases and hyaluronidase are being explored, but the regulation of these processes remains an area for investigation [9]. Perhaps the most direct strategy to preserve the glycocalyx is avoidance of conditions likely to damage the glycocalyx including hypovolemia and associated reperfusion injury. Thus fluid therapy that aims to maintain tissue perfusion is likely to be protective of the glycocalyx. On the other hand there is evidence that excessive fluid infusion leading to hypervolemia results in damage to the glycocalyx due to the release of atrial natriuretic peptide [55] although the mechanism of action is not clear because ANP can also have vasoprotective actions [56–58].

As these and other approaches are evaluated in more detail in different clinical settings there is a need for new strategies to assess the integrity of the glycocalyx. In addition to the development of better assays for glycocalyx components in the plasma as suggested above, more direct methods are currently being actively promoted. One of the approaches involves attempts to measure the volume of the glycocalyx by comparing the volume available to tracers assumed to penetrate the glycocalyx from the volume of circulating plasma. The second approach uses direct

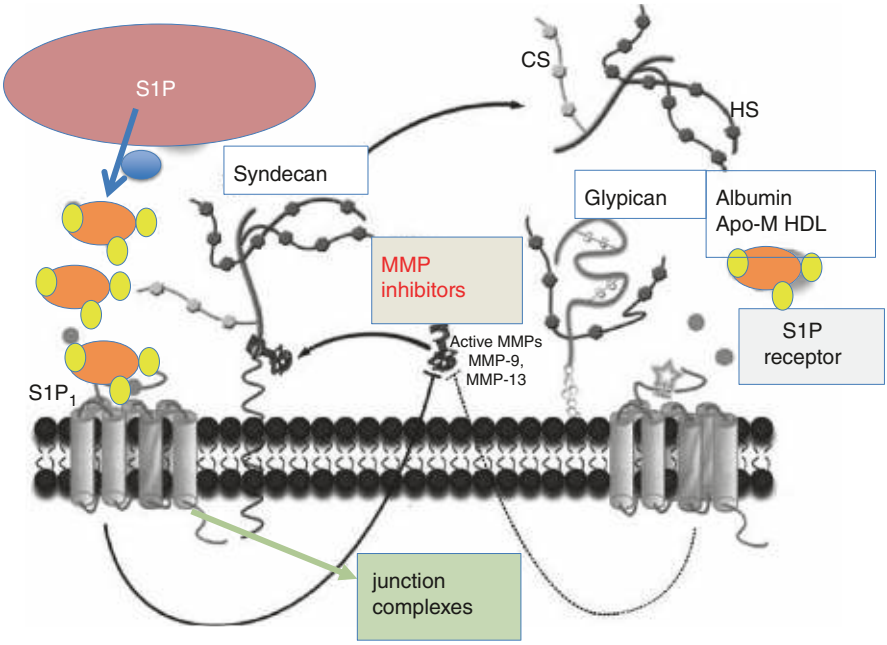


Fig. 3.3 The roles of sphingosine-1-phosphate (S1P) and albumin to stabilize the glycocalyx. S1P is stored in circulating red cells, released into the circulation bound to albumin and Apolipoprotein-M in HDLs. Ligation to the S1P1 receptor on endothelium activates signaling pathways that regulate the stability of the inter-endothelial cell junctions, inhibits MMP activation, and abolishes MMP dependent syndecan-1 ectodomain shedding. Conditions that reduce S1P availability (e.g. low plasma protein) have been demonstrated to attenuate the inhibition of MMP9 and MMP13 and result in loss of the glycocalyx. S1P also stabilizes the inter-endothelial junctions. Adapted from [45] with permission

visualization of the small vessels in the sublingual microcirculation to measure changes in the penetration of red cells into the endothelial surface layer as a marker of glycocalyx loss. To enable evaluation of these new approaches it is useful to review current understanding of the 3D structure of the glycocalyx, based on investigations using electronmicroscopic methods, a range of optical techniques, and 3D image reconstruction approaches.

Imaging the Glycocalyx and Structure-Function Relationships

Of the vast number of imaging techniques available, the most useful for imaging the glycocalyx are optical microscopy (OP) with its dynamic and fluorescent capabilities, and electron microscopy (EM) with its molecular resolution and newer 3D structural capabilities. Other imaging approaches such as atomic force microscopy and magnetic resonance imaging have been less useful. Both OP and EM approaches have significant limitations. The dimensions of the glycocalyx are on the limit of the

resolution of optical microscopy that has a theoretical value close to 200 nm. This level of resolution is not reached when the glycocalyx is examined in wet biological samples. Similarly, the theoretical resolution of electron microscopy (<0.01 nm) is not reached in biological samples prepared by fixation and imbedding in plastic resins. Furthermore, sample preparation for electron microscopic analysis can result in loss of key components depending on the fixative and subsequent processing. What is actually visualized after such additional sample processing depends on the degree to which key components are retained and the chemical interaction of specific stains with these components. Further details of imaging methods are in Section "Background: Imaging the Glycocalyx: More Detailed Technical Issues", and we have included some Top Tips boxes to help follow the interpretation of the evidence discussed.

Top Tips: Interpreting Imaging Research

There are some important things to remember when evaluating imaging data highlighted in this chapter

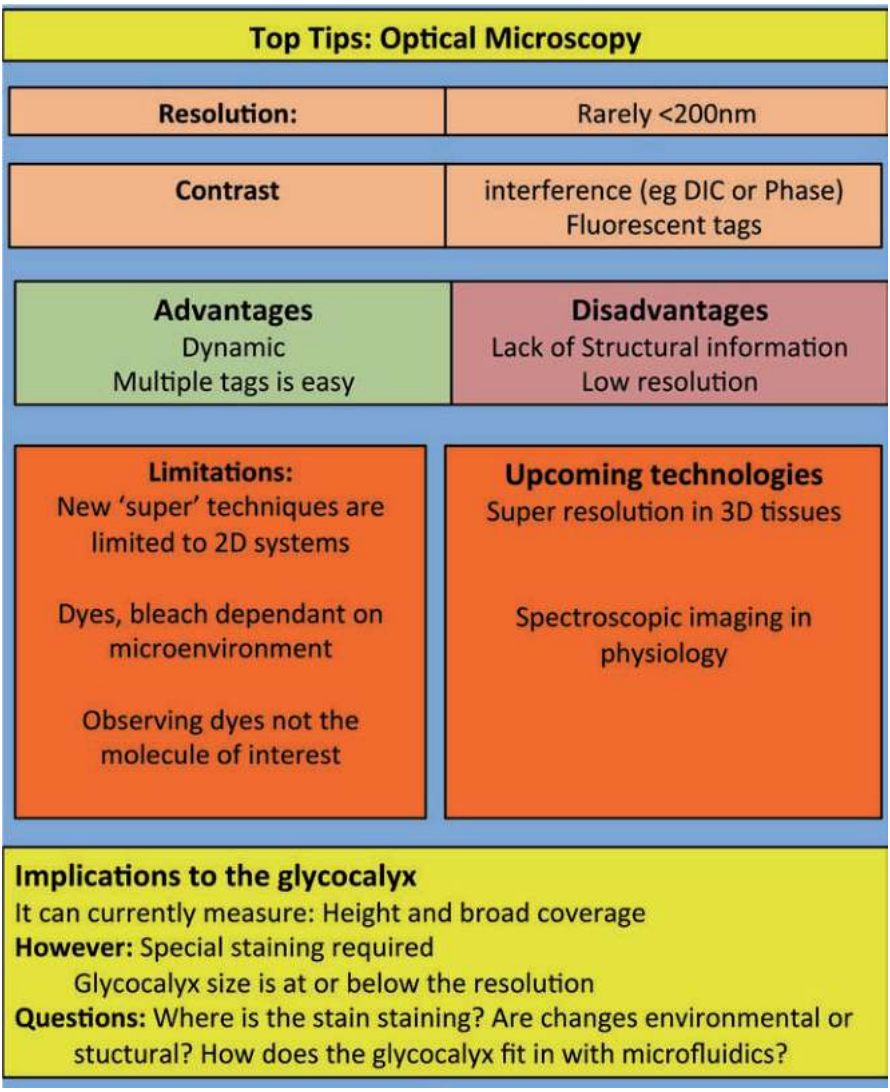
Resolution is the distance that two objects can be apart and still observe them as two objects not one. This is approximately half the wavelength of the beam, so ~200nm for a light microscope, ~40nm for X-Ray microscope, ~0.003nm for an electron microscope. However electron optics is very inefficient therefore <1nm is performing well.

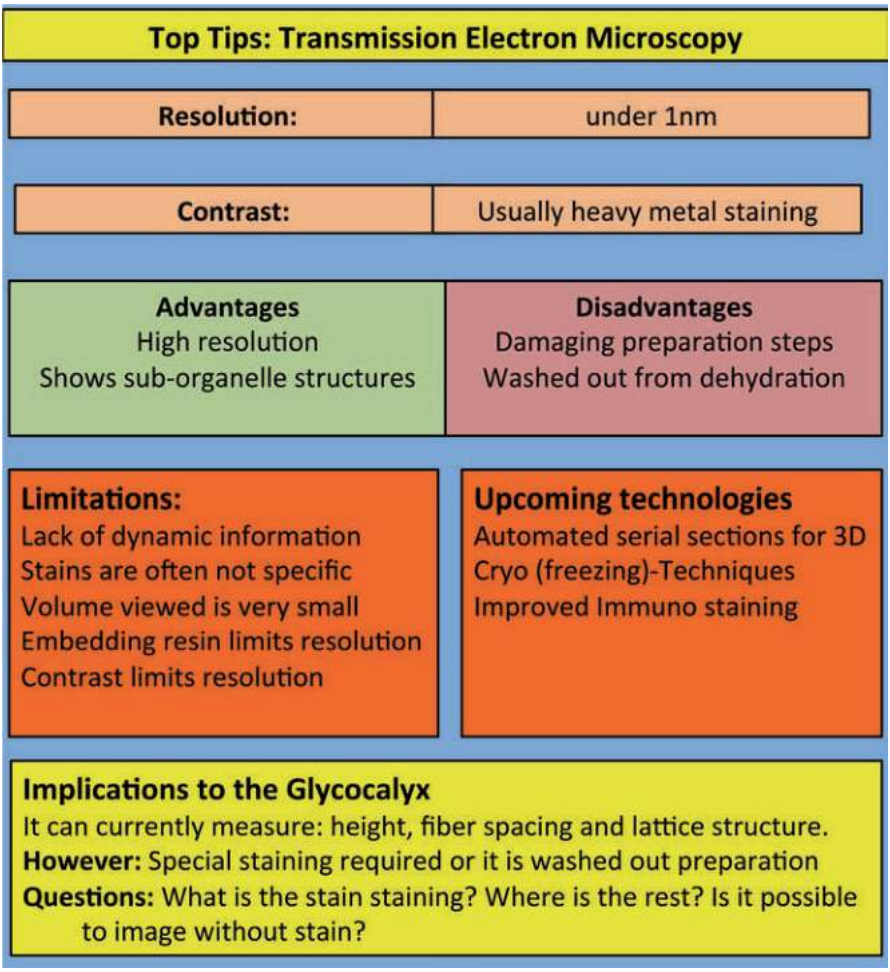
Contrast is not resolution. It is effectively the signal to noise, i.e. how easily one can observe an object, and this depends on the objects interaction with the beam compared to the surroundings. It is possible to observe an object much smaller than the resolution.

What you see is not the truth! One observes the interaction between the beam, the object of interest and any other objects.

For example: A fluorescent point is where there is an interaction with an object at the time it was imaged.

In itself this is not: The tagged molecule, dynamic, structural, functional or natural. On top of this there is quenching, bleaching and any changes the tag makes to the molecule of interest.


Top Tips: Optical Microscopy
Resolution:
Rarely <200nm
Contrast
interference (eg DIC or Phase)
Fluorescent tags
Advantages
Dynamic
Multiple tags is easy
Disadvantages
Lack of Structural information
Low resolution
Limitations:
New 'super' techniques are limited to 2D systems
Dyes, bleach dependant on microenvironment
Observing dyes not the molecule of interest
Upcoming technologies
Super resolution in 3D tissues
Spectroscopic imaging in physiology
Implications to the glycocalyx
It can currently measure: Height and broad coverage
However: Special staining required
Glycocalyx size is at or below the resolution
Questions: Where is the stain staining? Are changes environmental or stuctural? How does the glycocalyx fit in with microfluidics?



When our understanding of the permeability properties of the vascular wall was first put on a sound quantitative basis using the pore theory of capillary permeability [59, 60] it was suggested that the physical structures that were described in terms of water and solute exchange though "pores" were actually the interstices in the intercellular cement. At the level of light microscopy the "cement-like" substance appeared to be associated with the endothelial cell surface and parts of the junctions between endothelial cells. Early electron microscopists rejected the idea of this intercellular cement because none was found in the early investigations of junctions of microvessels in tissue fixed for electron microscopy. Instead they focused attention on barriers within the junctions and on specialized transport pathways associated with the endothelial caveolae. It required the systemic studies of investigators like John H Luft to demonstrate that chemical reactions between fixatives such as glutaraldehyde, contrast agents such as osmium tetroxide, and complex compounds

such as ruthenium red could be used to demonstrate a dense endocapillary layer that extended several 10s of nanometers into the vessel lumen and then faded in a fluffy indeterminate boundary [61]. This endocapillary layer was seen adhering to the outer leaflets of the luminal endothelial cell membranes and also extended into the luminal aspect of some junctions and openings of luminal vesicles. Botanists had previously used compounds such a ruthenium red to stain the acid mucopolysaccharides on the surface of plant cells so it was concluded that similar compounds as well as other plasma components formed the endocapillary layer.

As indicated above these early observations of a surface glycocalyx did not significantly modify the idea, current in the late 1960s, and well into the 1980s, that the size limiting structures in the endothelial barrier, corresponding to the small pores of classical pore theory, resided within the narrow constrictions of the junctions between adjacent endothelial cells. However, by the mid-1980s two independent lines of investigation refocused attention of the glycocalyx at the microvessel level (some of the extensive background to these studies is reviewed in the first Handbook of Microcirculation, published in 1984 [62–65]). One was the formal development of a quantitative framework to evaluate the permeability properties of a fiber matrix on the endothelial surface. Curry and Michel [66] demonstrated that a matrix with fiber dimensions similar to the side chains of glycosaminoglycans would offer little resistance to low molecular weight nutrient solutes as they crossed via the interendothelial junctions, but would form the primary barrier to plasma protein at the endothelial cell surface. Equally important were renewed experiments to understand the mechanisms whereby vascular permeability to water and macromolecular solutes was increased when plasma proteins such as albumin were removed from perfusates. In the absence of albumin or plasma, the permeability of the endothelial barrier to water and large molecules was increased without significant change in the structure in the junctions. When the cationic arginine groups on albumin were chemically shielded, albumin no longer maintained normal low permeability consistent with the theory that electrostatic interactions of albumin with the negative charged glycosaminoglycan side chains contributed to glycocalyx stability and organization (See [67]). An additional "proof of concept" result was that cationic ferritin, a large protein that could be visualized in EM sections when bound to the endothelial surface as the result of its large positive charge, formed a layer on the endothelial surface similar in thickness to the observed glycocalyx structure, and restored permeability after albumin was removed.

The second line of investigations focused on the mechanism determining red cell and plasma flows within microvessels, and the suggestion that a red cell free plasma layer close to 0.5 μm thickness must be present near the walls of cremaster muscle microvessels to account for the measured microvessel hematocrit [68, 69].

A series of key observations that still form the basis for many current investigations and clinical approaches to investigate the glycocalyx were made by Brian Duling and his colleagues in small blood perfused vessels in situ [70]. As shown in Fig. 3.4 they demonstrated that large Dextran molecules (MW greater than 70 kDa) were excluded from a plasma layer of thickness (0.3–0.5 μm) close to the microvessel walls. The dimension of this plasma layer was similar to the layer from which

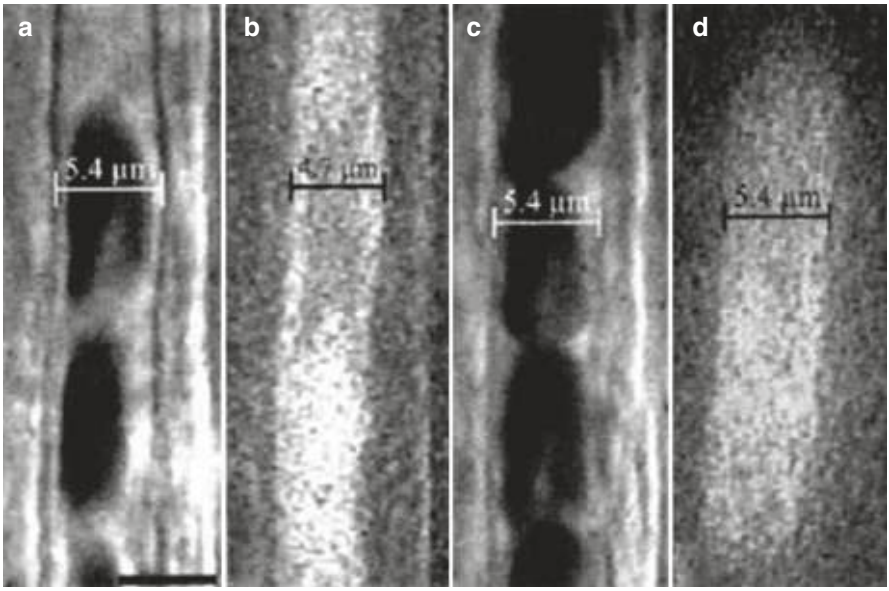


Fig. 3.4 The endothelial glycocalyx excludes large macromolecules such as 70 kDa dextran and circulating red cells. Parts A and B show digitized images of a capillary segment in a normal vessel. The width of both the blood cell column (A) and the column of high molecular weight FITC-dextran (70 kDa) (B) were significantly smaller than the anatomic capillary diameter. Damage to the glycocalyx (exposure of the capillary to epi-illumination with generation of free radicals) increased the width of RBC (C) and the FITC-dextran columns (D), without a significant effect on the anatomic capillary diameter. Scale bar represents 5 μm. Reproduced with permission [70]

red cells were excluded. Smaller neutral and cationic test probes slowly penetrated the barrier. Injury to the glycocalyx (e.g. by exposure to additional epi-illumination) decreased the region from which dextran and red cells were excluded. The idea that an extended glycocalyx structure might determine both the red cell exclusion gap by forming part of a lubrication layer and also a porous barrier that excluded circulating macromolecules was established after it was demonstrated that enzymes that degraded HS increased the penetration of both red cells and large dextrans (70 kDa MW) into the endothelial surface layer [29, 68, 70]. It was soon common to assume that an endothelial surface layer measured using these light microscopy approaches (up to 0.5 μm thick in capillaries) measured the full extent of the membrane-attached glycocalyx, and to dismiss the less extensive glycocalyx structures observed in electron microscopy as the collapsed forms of this more extended glycocalyx.

These observations also led to the idea that movement of test molecules from circulating plasma into the glycocalyx was a restricted diffusion process largely dependent of their size and charge. This ignores the fact that the time constants for penetration of albumin and dextrans (>40 kDa, <70 kDa) from the plasma into the endothelial surface layer were of the order of tens of minutes, far longer than

expected due only to electrostatic exclusion and restricted diffusion. For example if the restricted diffusion coefficient of albumin was only 1% of its free value, the half time for penetration into a 1 μm thick layer would be about 1 s, two orders of magnitude faster than observed. Further, a large molecule such as 70 kDa dextran, which did not normally penetrate the layer, when linked to albumin entered the layer despite the increased molecular size of the complex. Together with more recent evidence that different enzyme treatment results in differing degrees of penetration of tracer molecules into the glycocalyx [71], these observations indicate that complex diffusion, binding and chemical interactions compromise simple interpretations of tracer penetration and distribution in the glycocalyx (see Section "Glycocalyx Volume Measurement in Human Subjects" on the measurement of glycocalyx volume).

In summary, by the end of the 1990s there was a clear understanding that the glycocalyx was a key regulator of microvascular function because it played a major role to regulate plasma and red cell flows through microvessels and to form the main molecular sieve determining the exchanges on plasma constitutes and particularly the plasma proteins between circulating blood and the body tissues. At the same time it was apparent that the advances that had enabled visualization of this endocapillary layer provided only a low-resolution image of the structure of the glycocalyx and pointed to the difficulties that investigators still face today to quantify changes in the glycocalyx structure.

The Glycocalyx as a 3 Dimensional Layered Structure in Microvessels

As explained in more detail in Section "Background: Imaging the Glycocalyx: More Detailed Technical Issues" and in the adjacent side bars there have been important technical developments that not only improve the preservation of the glycocalyx, but enable more detailed investigations of the glycocalyx as a 3D quasi-periodic structure within a region 200–400 nm of the endothelial surface. Figure 3.5 based on samples from Rostgaard and Qvortrop [72] demonstrates bush-like structures in the glycocalyx that project 100 nm from the fenestrated endothelium of rat small interstine and post-glomerular microvessels. These structures were preserved using a novel perfluorocarbon perfusion technique. Figure 3.6 summarises results from the first application of computer autocorrelation functions and Fourier transforms of EM images from frog mesentery capillaries fixed by both conventional fixation and rapidly frozen, deep-etched preparations of glycocalyx. The analyses demonstrated a network of fibrous molecules with a characteristic interfiber spacing of 20 nm and fiber diameter of 12 nm. Additional investigations on these preparations showed that the regularly distributed fibers occurred in clusters with a common intercluster spacing of ~100 nm. The result that similar measurements of fiber size, spacing, and arrangement were made in preparations made without exposing the tissues to chemical fixatives as well as those prepared using conventional fixation and staining techniques indicated that there was a common quasi-periodic

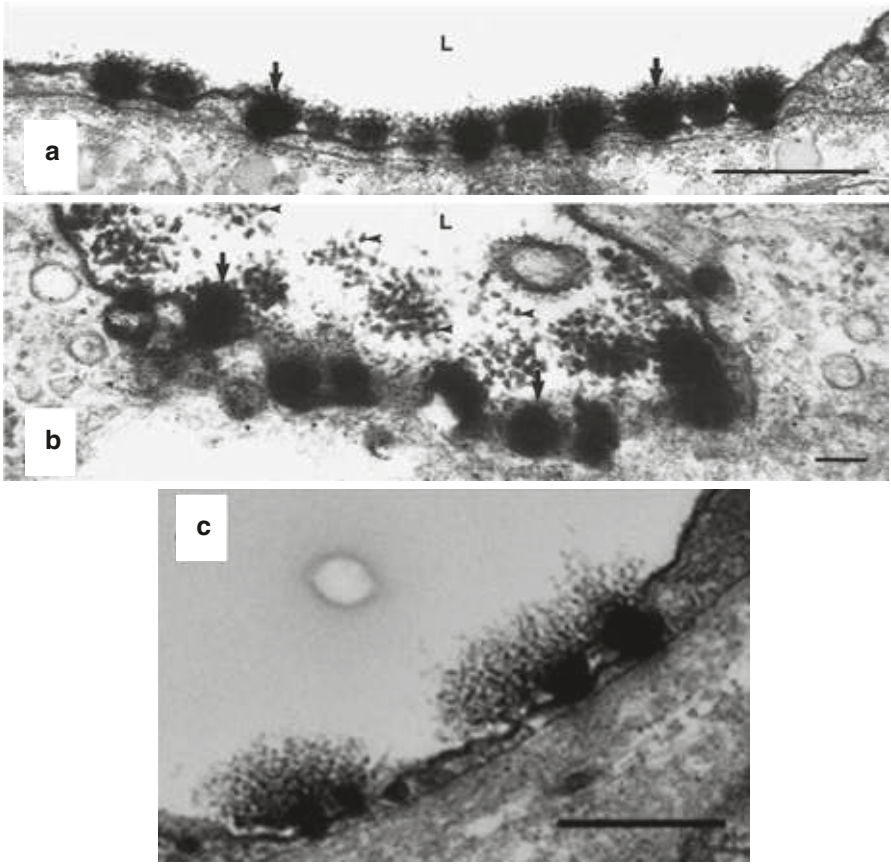


Fig. 3.5 Examples of bush-like structures in the glycocalyx first described in electron micrographs of fenestrated capillaries from the lamina propria of rat small intestine (**a** and **b**) and glomerulus (**c**). The tissue was processed using perfusion fixation with a perflurocarbon perfusate, glutaraldehyde as fixative, and tannic acid for staining. Part A shows the bushes projecting into the capillary lumen about 150 nm. Part B is a tangential section showing filamentous molecules (5–10 nm thick) forming the bushes with 20–40 molecules per bush. Part C is similar to A from rat glomerulus. Scale bar in A and C is 0.5 μm, in B is 0.1 μm. These bush like structures observed in TEM have guided the interpretation of autocorrelation analyses of images of the glycocalyx to reveal the quasi-periodicity of molecular structures of the inner glycocalyx. Reproduced with permission from [72]

structure to the inner glycocalyx. Using the regular bush-like structure observed in the original Rostgaard and Qvortrup study [72] as a guide, Squire and colleagues [17] proposed a structural model of the glycocalyx in which the available space for macromolecule movement between the fibers in a cluster was close to 8 nm. This dimension was determined within bush-like bundles by fibers (12 nm in diameter) arranged at 20 nm mean interfiber spacing. They also suggested that the 100 nm intercluster spacing reflected attachments by transmembrane proteins to a

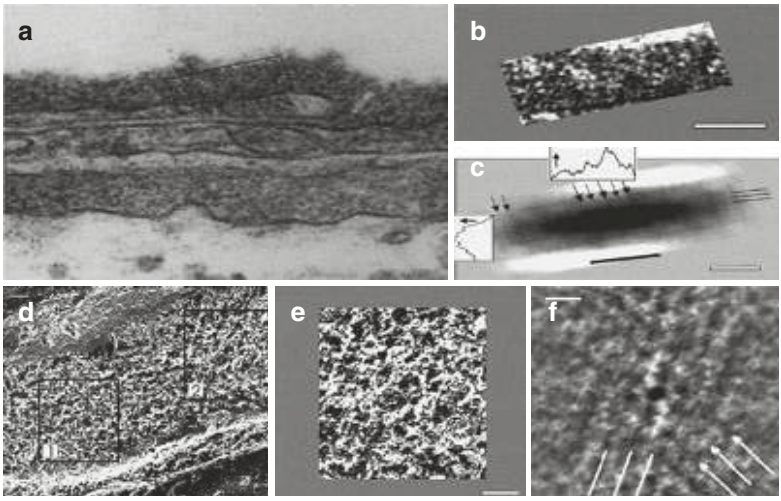


Fig. 3.6 The top panel shows regions of a normal capillary from frog mesentery prepared using conventional fixations. Individual microvessels were perfused with Ringers solution containing 4% bovine serum albumin and ruthenium red prior to fixation with 1% osmium tetroxide (**a**). The boxed region is shown enlarged in **b** and the results of auto-correlation analyses in **c**. The analysis indicates periodicities in directions parallel to the luminal endothelial surface and normal to the surface. The lower panel shows images from a frog mesentery microvessel rapidly frozen, and freeze fractured to show the inner region of the glycocalyx. The autocorrelation analysis of the boxed region demonstrates hexagonal arrangement of the spacing of larger structures 80–120 nm apart (see lines and arrows). Smaller periodicities of around 20 nm are seen within these major repeats. The similarity of autocorrelation functions from tissues after different fixation and staining protocols, and from both frog and mammalian vessels suggest a common quasi-periodic structure of the inner glycocalyx. Scale bars 200 nm in **a**, 60 nm in **b** and 110 nm in **c**. Scale bars are 200 nm in **d**–**f**. Modified with permission from [17]

quasi-regular submembrane actin network. These investigations gave, for the first time, evidence of a more organized structure of the glycocalyx within about 200 nm of the endothelial surface with anchoring foci that appear to emanate from the underlying actin cortical cytoskeleton, a concept supported by biochemical evidence [73–75]. A sketch of this ultrastructural model is shown in the left panels of Fig. 3.7.

A similar approach performed on archival tissue samples from Rostgaard and Qvortrup's laboratories [76] also found an interfiber spacing of 19.5 nm to be common within fiber clusters in many different tissues from rats and rabbits. Taken together with the results in frog vessels, these analyses based on autocorrelation methods suggested that an interfiber spacing close to 20 nm was likely to be a common characteristic of regions of the glycocalyx that were organized into quasi-periodic arrays. However though spacings over 80 nm were observed the 100 nm previously observed was not one of them, perhaps due to amalgamating the fenestrated and unfenestrated tissues into one result. Interpretation of the longer distances remains inconclusive, and to definitely demonstrate it solely by this method,

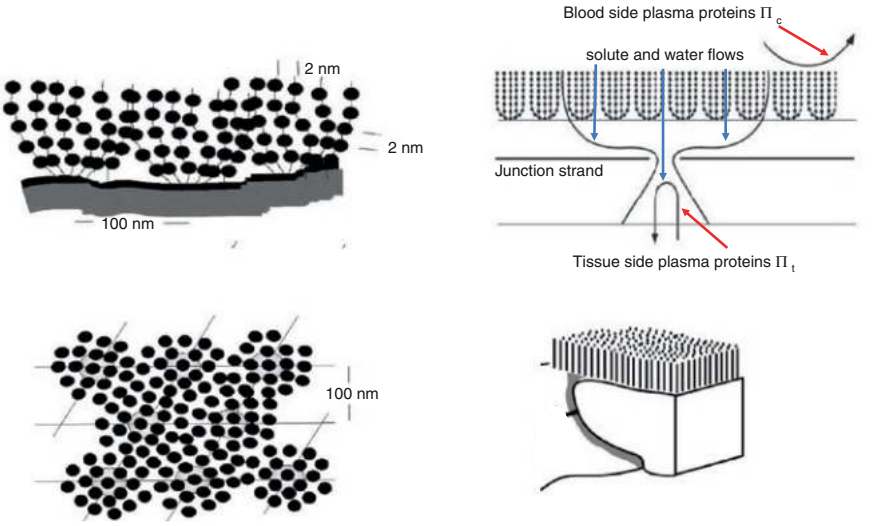


Fig. 3.7 Model molecular configuration of the inner glycocalyx is shown in the sketches on the left showing fibrous strands projecting from the endothelial surface with some periodicity along the strands. Adjacent tufts are separated by 80–100 nm in a hexagonal array. A more formalized schematic is shown on the right with the geometric arrangements assumed for detailed quantitative analysis of transendothelial water and solute exchange through the glycocalyx and intercellular junctions, and red cell movement over a lubricating layer formed by the glycocalyx. Adapted from [8, 17]

without additional specific labeling, may not be possible. Nevertheless in the sketch in Fig. 3.7 it is assumed to be characteristic of the inner regions of the glycocalyx in both non-fenestrated and fenestrated microvessels and measurements and conclusions based on these studies are quoted in several review papers and used in mathematical models [1, 5, 8]. As indicated above, the evidence is still quite limited and there are technical limitations to the interpretation of autocorrelation analyses based on projections through thick specimens. Furthermore, a more useful "en face" view of the glycocalyx cannot be obtained from these approaches which give mainly a sideview of the glycocalyx (See Section "Background: Imaging the Glycocalyx: More Detailed Technical Issues").

As a step towards better 3D imaging of the glycocalyx a recent study used electron tomographic methods to examine the glycocalyx [77]. Here images from thicker 300 nm plastic sections were taken at many different angles enabling reconstructing into a 3D dataset. The resulting reconstructions not only allow comparison with the autocorrelation approach described above, but also allow the image to be rotated to enable en face observation of the lateral spacing of the anchoring foci on the endothelial surface in mammalian microvessels (both continuous and fenestrated). The method can therefore offer further evaluation of the periodic structure of 10–12 nm diameter fibers and any characteristic longer spacing of around 100 nm. As new analyses become available there is a growing consensus that a quasi-periodic

structure that projects at least 50 nm and up to 400 nm from the endothelial membrane is present and can, to a first approximation, be characterized by the idealized mathematical model with hexagonal symmetry shown on the right of Fig. 3.7. For further details of the strengths and limitations of these methods see Section "Background: Imaging the Glycocalyx: More Detailed Technical Issues".

Quantitative Investigations of Glycocalyx Structure-Function

A key question is to understand how there can be, on one hand, an endothelial surface layer equal to or greater than 0.5 μm in thickness from which red cells are excluded, yet on the other hand ultrastructural analyses describe structures closer to the endothelial surface that have the properties of a molecular sieve. The hypothesis that a layered structure consistent with the inner semi-periodic structure and an outer less porous layer, likely stabilized by hyaluronic acid and adsorbed plasma proteins, can be tested using the model in Fig. 3.7. The approach with an emphasis on the inner structure has been reviewed in detail elsewhere [5, 6, 8, 45], and the main conclusions relevant to this chapter are summarized below.

With respect to trans-vascular exchange, the water filled spaces between the fibers in the quasi-periodic arrays forming the periodic array in Fig. 3.6 have similar molecular dimension to plasma proteins such as albumin. The combined effect of steric exclusion and electrostatic interactions between albumin and the fibers results in high resistance to plasma protein exchange across the glycocalyx and a large concentration difference of plasma protein between the circulating blood and the space beneath the glycocalyx. The main colloid osmotic pressure difference, which opposes the hydrostatic pressure difference between blood and tissue, is therefore across the glycocalyx. At high filtration rates (when microvessel pressure exceeds the effective colloid osmotic pressure of the plasma proteins) the ultrafiltrate of plasma (with a low plasma protein concentration) flows into the intercellular junction below the glycocalyx from where it is funneled through infrequent breaks in the strands of tight junction proteins that effectively seal off most of the perimeter of the endothelial cells. This maintains a plasma protein concentration difference across the glycocalyx that is larger than that between blood and the interstitial space. At lower pressures some of the plasma protein in the interstitial space does diffuse back into the space below the glycocalyx, but plasma protein concentration in the protected space below the glycocalyx always remains less than in the interstitial space as it is diluted by the ultrafiltrate [78–80] The result is a steady state balance between the hydrostatic and colloid osmotic pressures across the glycocalyx to maintain slow filtration as described in Chap. 2 on the Revised Starling Principle.

An example of the gradients of albumin concentration at high and low filtration rates is Fig. 3.8 (From [81]). The figure emphasises the importance of maintaining the integrity of the glycocalyx. The effectiveness of the colloid osmotic pressure difference across the glycocalyx to oppose the hydrostatic pressure difference between blood and tissue and maintain low filtration is reduced when the glycocalyx is damaged or lost. Furthermore, it is important to stress that the primary

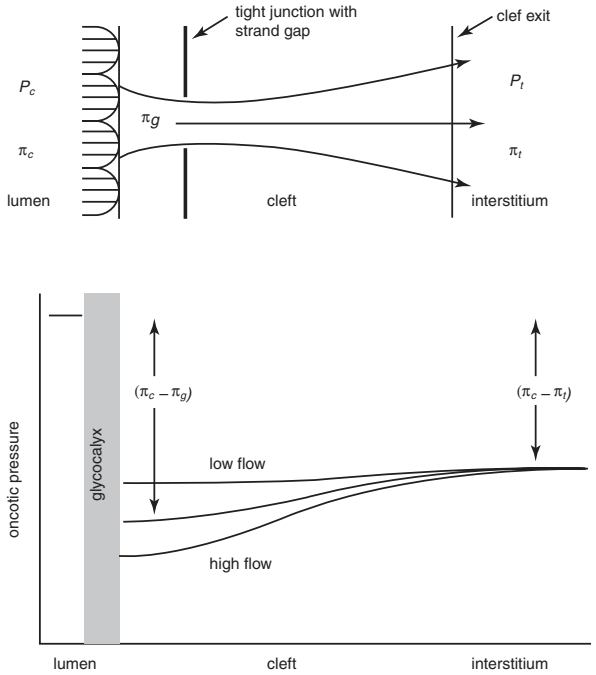


Fig. 3.8 Model demonstrating that the osmotic pressure of the subglycocalyx region is always lower than that in the mixed interstitial fluid in a filtering microvessel. The ultrafiltrate crossing the normal glycocalyx has a low plasma protein content. When funneled into breaks in the junctional strands this ultrafiltrate reduces diffusion of plasma proteins from the interstitium. This maintains a larger effective plasma protein osmotic pressure difference across the glycocalyx than that across the whole endothelial barrier (the blood to tissue protein concentration difference). From [81] with permission

pathways for water exchange are the intercellular junctions in the endothelium of continuous capillaries and the fenestrae in fenestrated capillaries. In continuous capillaries (lung, heart, skin, muscle) less than 1% of the area of glycocalyx lies over the line of contact between adjacent endothelial cells and even less is associated with the infrequent breaks in the junctional strands within the junctions. A critical assumption in the models of Figs. 3.7 and 3.8 is that the composition and structure of the glycocalyx in the region of the primary water pathways is the same as that observed over the other 99% of the endothelial surface. In fenestrated capillaries, the fraction of the endothelial surface that forms the transcellular water pathway is larger, but the glycocalyx structure in the region of fenestrae is assumed the same as that observed over at other sites on the endothelium (as in Fig. 3.7).

In parallel with the use of the model in Fig. 3.7 to evaluate water and solute exchange, the role of the glycocalyx to modify plasma and red cell flows along microvessels has been extensively investigated by a number of investigators. Of particular importance is the idea that the movement of water within the glycocalyx in the direction of blood flow is also restricted by the fibers. Via this mechanism, the

glycocalyx forms a "lubricating layer" which reduces the friction between red cells and the microvessel wall. This lubricating layer must cover the whole endothelial surface to be effective. Thus one way to test whether properties of the glycocalyx characteristic of the whole endothelial surface also describe fluid exchange through the more localized junctions or fenestrae is to use the results of calculations by Weinbaum et al. and others [80, 82, 83] to test whether estimates of resistance to water flow across the glycocalyx (i.e. during trans-vascular exchange) can also account for the properties of a functional lubricating layer. For example, the Darcy coefficient (K_w, a measure of conductance to water flow) has values in the range 10^{-13} to 10^{-14} cm^2 associated with the periodic structures close to the membrane of Fig. 3.8 (within 200 nm of the surface). According to Weinbaum et al. [83], layers 200 nm thick or greater are sufficient to describe an effective lubrication layer mechanism for red cells. This mechanism would be similar to the way a skier using a hard flat ski crosses powdered snow.

The results of this analyses [1, 8, 78, 81] demonstrate a consistent description of the glycocalyx as both a permeability barrier and an effective lubricating layer with glycocalyx thicknesses in the range of 200–400 nm. The structure has a quasi-periodic structure imposed by direct or indirect association of glycocalyx components with the endothelial cell cytoskeleton and cell membrane and binding of plasma protein components including albumin (Figs. 3.7 and 3.2). To a first approximation this seems a reasonable view of the glycocalyx in mammalian microvessels less than 5 μm in diameter such as those investigated by Vink and Duling (Fig. 3.4). However, this analysis requires further evaluation. For example the "skiing" analogy does not take into account the contribution of the red cell glycocalyx. In model systems the dual glycocalyx interaction has been demonstrated to be important, so the criterion based only on the endothelial glycocalyx properties may need to be modified [84, 85]. Further, in continuous endothelium, it will be important to understand how changes in adhesion complexes that regulate the stability of intercellular junction [45] may also modify the quasi-periodic structure of glycocalyx components attached to the cytoskeleton in the region of the junctions.

Direct and indirect measurements that suggest a glycocalyx thickness greater than 0.5 μm in larger micovessels (see Sections "Measurement of Red Cell Gap in Human Subjects" and "Glycocalyx Volume Measurement in Human Subjects") also highlight fundamental gaps in our knowledge about the uniformity of glycocalyx structure and composition. While a two to five fold increase in thickness of a glycocalyx layer with the same properties as described above would support red cell flows, and reduce leukocyte interactions with the endothelial cell, the same increase in thickness predicts a reduction in trans-vascular water movement to well below all measured values in microvessels [65]. There are several ways to resolve this problem, all involving assumptions about the composition and distribution of the glycocalyx components at a distance greater than 300–400 μm from the endothelial surface. One of the simplest assumptions is that the outer layers of the glycocalyx (thickness L) have less resistance to water flows than the inner layers. Curry and Michel [86] have evaluated the functional properties of the bi-layer model shown in Fig. 3.9. It has an inner structure with permeability

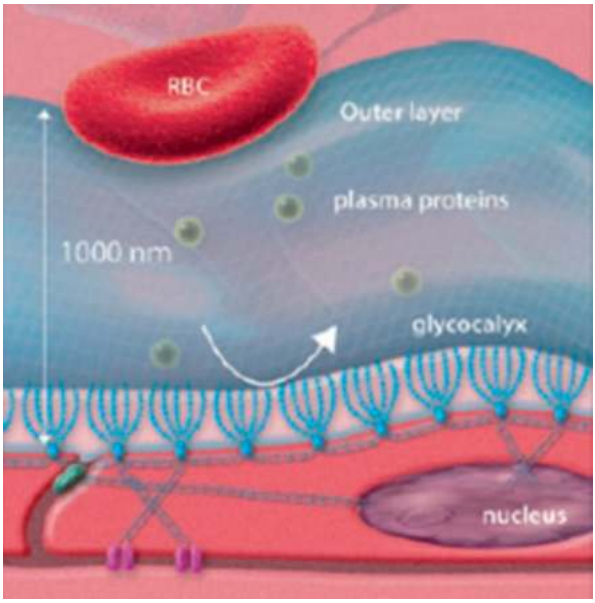


Fig. 3.9 Cartoon to illustrate a bi-layer model of the endothelial glycocalyx. The inner layer is a quasi-periodic matrix associated with bush-like structures with spacings between fibers similar to the dimensions of albumin. as in Fig. 3.7. This layer forms the primary molecular sieve at the microvascular wall. As drawn the bush like structures that are anchored to the cell cytoskeleton represent syndecan molecules which have heparan sulfate and chondroitin sulfate attached as side chains and extend up to 200 nm from theendothelial surface. The outer gel-like layer is more porous and assumed to have some of the characteristics of a hyaluronic acid solution . This layer forms a "lubrication layer" for the movement of red cells . Red cells and endothelial cell dimensions are not to scale. In a small capillary the red cell would be curled in on itself and would apply pressure to the outer layer as part of its functions as a mechanotransducer. From [87] with permission

properties similar to those associated with the glycocalyx in Fig. 3.2, but with an outer layer with increased porosity.

For example, the criterion for an effective lubrication layer ($L/K_w^{0.5} > 100$) is met with an outer glycocalyx thickness up to 1 μm but with a hydraulic resistance more that an order of magnitude less than the inner core. In such a bi-layer the normal range of permeability properties is accounted for if the outer layer also has permeability to albumin more than 20 times higher than that of the inner layer. This property ensures that the tendency for albumin to accumulate at the boundary between the outer layer and the more restrictive inner layer is reduced by rapid diffusion of accumulated albumin back into the circulation. The composition of outer glycocalyx layers that extend more than 5 μm from the endothelial surface is not well understood. Curry and Michel [86] assumed that hyaluronic acid was a principal component because individual molecules can be more that 1 micron in length. However as suggested by the top panel of Fig. 3.2 the composition of the outer layer is likely be determined by a dynamic balance between loss of glycocalyx

components, binding of circulating plasma components and ongoing synthesis of key components by the endothelial cells.

It is important to evaluate such models, not only to further understand fundamental glycocalyx structure-function relations in larger microvessels, but also because these models suggest that changes in the thickness and distribution of the outer layer may not be representative of changes in the inner layer. Thus the methods developed for application in the clinic (such as measurements of glycocalyx volume and visualization of the layer from which red cells are excluded in sublingual microvessels) which often suggest a glycocalyx layer several microns in thickness may not measure changes in the glycocalyx that are characteristic of the core structure of the glycocalyx. By focussing on glycocalyx composition as a function of glycocalyx thickness, the bi-layer model is a specific example of a way to evaluate the assumption that the glycocalyx close to the main transvascular exchange pathways (both intercellular and transcellular, that together occupy less than 1% of total endothelial surface) has the same structure and composition as that measured over the rest of the endothelial surface. The bi-layer model places limits on the permeability properties of the outer layer that are compatible with measured transvascular exchange and thereby may be a useful guide for further evaluation of the layered structure of the glycocalyx. Promising approaches include the use of super resolution imaging methods such as those described by Fu and colleagues (see below) [88] when combined with fluorescence probes that can penetrate into the inner layers of the glycocalyx.

Measurement of Red Cell Gap in Human Subjects

To overcome some of the limitation of analyses of glycocalyx function that require either chemical analyses of glycocalyx components including proteoglycans, hyaluronan, or heparan sulfates (HS) in the plasma, and invasive and time-consuming methods using the distribution of labelled red blood cells (RBCs) and low-molecular weight dextrans, there has been a renewed focus on non-invasive tools for analysing the endothelial surface layers using methods such as sidestream–dark field imaging. This method is the development of methods introduced in 1990 to improve the contrast between red cells, the vessel wall and the background known as orthogonal polarization spectral imaging [89]. The orthogonal polarization spectral method was not developed initially for imaging the glycocalyx, but has been widely used to measure other characteristics of the microvasculature including capillary densities and an index of local microvascular flow [90]. However, the enhanced contrast between the boundary of the red cell column and the vessel wall has led to its application in the sublingual microcirculation of human patients. For clinical settings the aim has been to measure changes in the extent that red cells penetrate the normal cell free layer near the wall of microvessels. A critical assumption, based on the observations in small vessels such as those in Fig. 3.4 is that an increased width of the red cell column (or decreased cell free layer thickness) indicates loss of

glycocalyx. There has been a succession of reports describing the adaptation of the orthogonal polarization spectral approach as sidestream dark field imaging.

In some reports technical details are minimal but the approach appears to have been used in at least three forms [36, 43, 91, 92]. Version 1 measures an ESL thickness in small blood vessels (diameter <15 μm) as the space between the red cell column and the image of the vessel wall whose position is enhanced by computer image processing. Version 2 (Fig. 3.10), abandons measurements of the position of the vessel wall altogether and measures only the red cell column width at multiple sites (20 or more) along a microvessel segment. A statistical analysis of the distribution of red cell column widths is used as a measure of the access of RBCs into the cell free boundary layer. A perfused boundary region (PBR) thickness is defined as the difference between the mean red cell column width and a characteristic diameter of the region into which red cells penetrate, apparently derived from a statistical analysis based on the 25 and 75 percentiles of the red cell width distribution. This version is fully automated using software developed at the University of Amsterdam and blinded to the investigator. A third version, first described in detail in 2008 [36], compares the space available to red cells in the absence of rolling leukocytes to the transient increase in space available to red cells after leukocyte passage. The method is based on the observation that leukocytes, which are more rigid than red cells compress the capillary endothelial glycocalyx during their passage through the lumen, thus allowing a transient "widening" of the erythrocyte column [83]. The

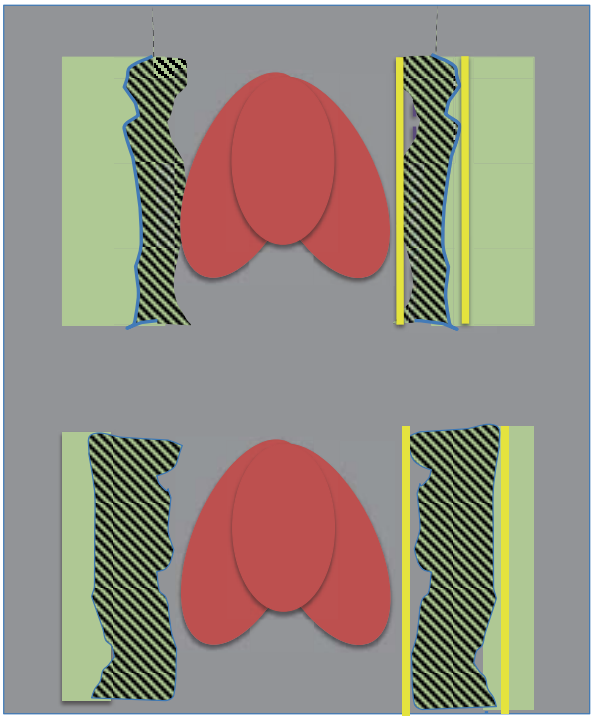


Fig. 3.10 The idea that red cells penetrate closer to the vascular wall when the glycocalyx is damaged in a capillary (as in Fig. 3.4) is being tested as a basis for sidestream dark field imaging in microvessels up to 50 μm diameter in the sublingual vessels of human patients. The dimensions of a perfused boundary region (shown as a hatched region, and defined as the region between the yellow bands) in the microvessel is estimated from the distribution of diameters of the region accessible to red cells at many sites along a microvessel, and the median red cell column width during sidestream dark field imaging. Based on the description in [43]

change in erythrocyte column diameter observed during such widening divided by two is related to the dimension of the microvascular glycocalyx.

There have been several reports describing one or more of these approaches. In an initial paper [27], Nieuwdorp et al., using Version 3 in hamster muscle, reported the gap between red cells and the compressed glycocalyx to vary from 0.4 to 0.8 μm in vessels 4–8 μm diameter. These gap dimensions were smaller than the gap between erythrocyte and a measure of the position of the vessel edge (Version 1) suggesting the leukocyte did not penetrate right up to the vessel wall. They do fall in the same range as the measurements by other investigators in small blood vessels. The authors concluded that the technology provides values of the ESL that correlate well with the invasive technique based on tracer dilution in animal experiments (see below). Furthermore in the same report, PRB thickness evaluated in sublingual microvessels with mean diameter of 5.37 ± 0.45 μm in human subjects was 0.58 ± 0.16 μm. In a brief preliminary study it was also reported that the PRB layer was reduced in thickness in human patients in a variety of disease states.

The strategy of using Version 3 does not appear to have been followed up in any detail in spite of its being an interesting idea. Instead, application of version 2 to measure only changes in the penetration of red cells into the boundary region (PBR) has been reported in vessels less than 50 μm diameter. Some reported values are as follows: In vessels larger than 5 μm but less than 50 μm diameter, Vlahu et al. measured an increase in the perfused red cell column width from 16.4 μm in control subjects to 17.7 μm in dialysis patients [43]. There was no change in the reference red cell column width (10.5 in control vs 10.1 μm). The difference between perfused red cell column width and reference red cell column width indicated a statistically significant increase PBR (3.6 ± 0.4 μm compared with 3.3 ± 0.4 μm in healthy controls [43]. It was argued that the method was providing an index of glycocalyx loss; because the increase in PRB was measured in the same patients as where increased circulating levels of glycocalyx breakdown products were measured (e.g. the circulating HA and sydecan-1 levels reported in Section "Composition in Relation to a Layered Structure" were from the same patients). In other reports, patients with evidence of cardiovascular disease, PBR values were 2.2 ± 0.3 μm compared with 2.0 ± 0.3 μm in controls [69], and in chronically ill patients PBR was 2.7 μm (range 2.6–2.9) compared with 2.5 (range 2.4–2.7) μm in controls [70]. On the other hand Amraoui et al. found no correlation of PBR with cardiovascular risk [93]. The relatively small changes in PBR described in these studies raise questions about the power of the technique to discriminate diseased states from more healthy states, In spite of these concerns clinical evaluation of the non-invasive sublingual imaging has demonstrated inter-operator reproducibility and linked systemic vascular dysfunction with a variety of diseases including diabetes, sepis, systemic sclerosis and fevers [94, see also 95] As with all such developments, improvement can only be made when the key questions about the approach are addressed.

Sidestream dark field imaging methods assume that the change in the width of flowing red cells measures a real change in glycocalyx. Although there are independent estimates of endothelial surface layers extending several microns from the endothelial surface in large vessels (see below) there are reasons to question such

estimates as representative primarily of changes in the glycocalyx. For example, the well-known Fåhraeus effect describes the formation of cell free layers in microvessels in terms of the micromechanics of red cells, independent of interactions with a glycocalyx. Measurements independent of a surface layer (in glass microtubes), as well as theoretical models, demonstrate that a cell free layer several microns in thickness is expected in microvessels up to 50 μm diameter [96–99]. Furthermore, independent of changes in the glycocalyx, it is reasonable to propose mechanisms that may change the micromechanics of red cell movement within microvessels under inflammatory conditions (e.g. increased rolling and attachment of inflammatory cells, and the release and/or uptake of microparticles at the endothelial cell surface). In summary, the use of new optical techniques such as sidestream dark field imaging provides interesting new ways to evaluate changes in microvascular function. However claims that the sidestream dark field imaging approach, as currently applied, provides a specific biomarker of glycocalyx function particularly with regard to properties of the glycocalyx important in relation to peri-operative fluid therapy cannot be justified at this time. Nevertheless the idea that measurements of changes in red cell flow in easily visualized microvessels in human patients can be an aid to the diagnosis and treatment of chronic disease is an important area for further research, and further understanding of ways to evaluate the contribution of changes in glycocalyx structure and composition must be actively pursued. Examples of new investigations include comparison of results with other measurement methods on a vessel by vessel approach whilst modifying local red cell flows.

Glycocalyx Volume Measurement in Human Subjects

An alternate way to evaluate changes in glycocalyx function in human subjects has been to use measurement of a glycocalyx volume as a biomarker of glycocalyx. Two methods for estimating the volume of glycocalyx of the entire cardiovascular system have been described. Both depend on measurements of volume by the dilution of a tracer substance. It is important to revise the general principle and underlying assumptions of this approach in order to assess the value of these methods (see also Chap. 2).

The principle of estimating the volume of a fluid filled compartment from the dilution of a tracer is very simple: a known mass of a solute, m, is dissolved and mixed into the fluid whose volume is to be measured. After a short period of time, which is believed to be sufficient for complete mixing of the marker solute throughout the entire volume to be measured, the concentration of the solute in the fluid, C, is measured. Then since C = m/V,

$$\text{volume}, V = m / C. \tag{3.1}$$

The method should give the volume of the fluid in the compartment if two important conditions are met. These are: (1) all the tracer molecules are retained within the compartment at the time the concentration is measured and (2) at equilibrium, all the tracer molecules added to the system at zero time are at the same concentration in all regions of the compartment.

It is very rare for one to be able to assume with confidence that all the tracer molecules initially injected into a fluid compartment have all been retained there by the time its solution has mixed sufficiently in all regions to reach a uniform concentration. This is certainly not true when the tracer has been injected into the circulation and there is a standard way of dealing with it. Once it is thought that mixing within the circulation is complete, losses from the blood (or plasma) may be detected by serial measurements of tracer concentration. Providing the loss of tracer from the circulation is slow, it is reasonable to assume that initially it should follow an exponential decline and the logarithm of the concentration when plotted against time should describe a linear relation. This may then be back-extrapolated to zero time, when the concentration would be equal to that which would have been present if mixing throughout the compartment had been instantaneous. This estimate of concentration at zero time is then used with the total amount of tracer injected into the compartment to calculate its volume.

The second condition is too often neglected yet may easily be compromised for a range of reasons. For the entire tracer initially added to the compartment to be at the same concentration throughout the compartment, the tracer must not bind to any structures within the compartment. This would remove a fraction of its mass from solution and reduce the value of m in eq. (3.1).

Also, the tracer should be an uncharged molecule and have the same molecular size as water. If the tracer carries a negative charge, it may be excluded from regions of fluid closely bounded by surfaces or extracellular molecules which are themselves negatively charged. Alternatively, it may be concentrated in regions where bounding molecules carry a positive charge. Also, if the molecule is larger than water it will be excluded from regions of the compartment where the fluid filled spaces are comparable with or less than its own diameter to a greater degree than water molecules. Consequently its concentration in these regions will be lower than in more open regions. These phenomena are well known by investigators of interstitial fluids [100–102] and 60 years ago it was recognized that estimates of extracellular fluid volumes by tracer dilution were inversely proportional to the molecular size of the tracer (inulin giving the lower values and thiocyanate the higher ones). The condition of the tracer being the same molecular size as water is probably only approached when isotopes of water (either D_2O or HTO) are used as labels to estimate total body water.

The problem with estimating the volume of the glycocalyx is that the glycocalyx is a barrier to the diffusion of macromolecules. Therefore, even if a tracer, considerably larger than water, is able to penetrate the glycocalyx, it will be excluded from a significant fraction of the fluid phase within the matrix of fibrous molecules. To estimate the volume of the fluid within the glycocalyx, the partition coefficient for the tracer between the plasma and the glycocalyx must be known.

It may seem logical, therefore, to estimate the fluid volume within the glycocalyx using a tracer that is a small molecule and has a partition coefficient between glycocalyx and plasma close to one. Whilst small tracers may enter the glycocalyx from the plasma and distribute themselves rapidly within its fluid phase, they also diffuse rapidly out of it through the channels between the endothelial cells or through the

fenestrae into the much larger volume of interstitial fluid. In most, if not all, organs and tissues, the volume of the fluid phase of the glycocalyx is considerably less than the volume of the interstitial fluid (ISF) and because the rates of disappearance of small molecule tracers from the plasma and into the ISF are rapid, the transit time of tracer through the glycocalyx is too short to provide information of glycocalyx volume. If, however, once a small molecule had entered the glycocalyx, it was bound avidly to glycocalyx components and did not dissociate significantly and enter the interstitial space, it could be used as an indicator of glycocalyx volume. To estimate this quantitatively, once again one would have to know the partition coefficient of the tracer between the plasma and the glycocalyx. Then, the volume that one might calculate would be a virtual volume representing the number of binding sites on the glycocalyx on the luminal endothelia of the circulation and not the volume of the fluid phase within the glycocalyx.

Two methods for estimating glycocalyx volume have been published and both of them are open to criticism. The first of these methods was described by Nieuwdorp et al. and consists of measuring the initial volume of distribution of 40 kDa dextran (D40) [103], which it thought to enter the glycocalyx from the plasma giving a volume for the sum of the plasma volume and the glycocalyx volume. The plasma volume, estimated from the red cell volume and the large vessel hematocrit, is then subtracted from the distribution volume of D40, to give a value for the volume of the glycocalyx. Using this method in healthy volunteers, they obtained a mean value of 1.7 litres and a considerably lower value in patients with Type 2 diabetes. As pointed out [104], the method fails to meet the conditions of the dilution principle in several ways. First, the tracer, fluorescently labeled D40, appears to be a mixture of dextran polymers with an average molecular weight of 40 kDa. Consequently after its injection into the circulation, its disappearance from the plasma cannot be described by a simple exponential function over the first 10 min as dextran polymers of differing molecular weight leave the circulation at rates which are roughly inversely proportion to their molecular size. This gives rise to a considerable under-estimate of tracer concentration at zero time. Second, their use of the large vessel hematocrit to estimate plasma volume is uncritical and may lead to further errors (see below). Third, the authors assume the partition coefficient of D40 between the plasma and fluid phase of the glycocalyx to be one. This cannot be so because even the smaller D40 molecules are large compared with water molecules and should be excluded from the water surrounding the fibrous molecules within the glycocalyx. The larger D40 molecules should be severely excluded from the water surrounding the glycocalyx structures by a distance at least equal to the Stokes-Einstein radius of the D40 molecule. Since the glycocalyx acts as a molecular filter to macromolecules, the water within it is confined to spaces with widths comparable to those of the dextran molecules.

The importance of knowing the partition coefficient of the tracer molecule between the plasma and the glycocalyx can be illustrated by some simple algebra. If Cp and Cg are the equilibrium concentrations of a tracer in the plasma and the glycocalyx water and λ is the partition coefficient between glycocalyx and plasma. Then:

$$\lambda = Cg / Cp \tag{3.2}$$

If m moles of tracer are added to the plasma when time = 0, and all the tracer is confined to the plasma (volume = Vp) and the fluid phase of the glycocalyx (volume = Vg), at equilibrium (i.e. when mixing is complete):

$$m = CpVp + CgVg = CpVp + \lambda CpVg = Cp\left(Vp + \lambda Vg\right) \tag{3.3}$$

When eq. (3.1) is used to calculate the volume of distribution of the tracer, the desired result of estimating the sum of the volumes of the plasma and the glycocalyx water is obtained only if $\lambda = 1$, i.e.

$$m / Cp = Vp + \lambda Vg \tag{3.4}$$

Since λ is unknown, only λVg can be estimated by subtracting Vp from m/Cp. Furthermore, changes in the value of m/Cp are open to misinterpretation. If the thickness of the glycocalyx is reduced without change of λ, apparent glycocalyx volume, λVg, will be reduced and may be accompanied by increases of both hydraulic and solute permeabilities of vascular walls. Hydraulic and solute permeability might also increase if the glycocalyx were to expand, opening the water filled spaces within it and increasing λ for the tracer molecules and so amplifying the increase in apparent glycocalyx volume, λVg. The important lesson for the clinician is to regard conclusions reached by this method critically and wait until a sounder theoretical basis for the method has been established.

A second, more carefully argued, method for estimating glycocalyx volume is also open to criticism and misunderstanding [105, 106]. This method arose from measurements of red cell and plasma volume of patients subjected to pre-operative volume loading with colloid solutions, which were either 5% albumin or 6% hetastarch solutions [106]. It is argued that plasma volume estimated from the distribution volume of indocyanine green (ICG) can be divided into a circulating component and a non-circulating component. The non-circulating component is thought to be the glycocalyx or at least the plasma proteins (labeled with ICG) within the glycocalyx. By using fluorescently labeled red cells to estimate the total volume of red cells in the blood, the hematocrit, measured in blood taken from large vessels, is used to determine the circulating component. The volume of the non-circulating component of the plasma is calculated by subtracting the circulating component from the volume of distribution of the ICG. Rehm and colleagues [106] estimated mean values for non-circulating component in the range of 700 ml in patients before volume loading and 300 ml afterwards.

ICG is used routinely for estimating cardiac output, assessing liver function and for estimating plasma volume. After its injection into the circulation it binds rapidly but not covalently to plasma proteins (particularly albumin and lipoproteins). It is an anionic dye and there is a very low concentration of free dye present in the plasma in equilibrium with the bound ICG. It seems likely that this free dye rather than the dye-protein complex enters the glycocalyx and binds to structural molecules within it. Although the authors (of the method) speak of a dynamic equilibrium between proteins in the glycocalyx and those of the plasma, the relevant in vivo observations

made in hamster muscle capillaries [107] indicate that rates of penetration of labelled albumin and fibrinogen that would be negligible 2 min after their injection into the circulation. By contrast, a relatively small molecule, ICG could diffuse rapidly into the glycocalyx and if its affinity for sites there were high, near equilibrium concentrations could be rapidly established. This is a minor criticism.

Somewhat more questionable is the assumption that the large vessel hematocrit reflects the fractional volumes of cells and plasma in the circulating component of the blood. It has been known for over 80 years that the hematocrit measured on samples of blood taken from arteries or veins differs from that calculated from estimates of the total volumes of red cells and plasma [108]. Most of the earlier measurements of plasma volume were made using the dye Evans Blue (T1824), which like ICG is an anionic dye that binds rapidly but non-covalently to plasma protein. It is fair to assume that, like ICG, Evans Blue also binds to the glycocalyx and so that its distribution includes the non-circulating component. Further the Evans Blue (in both its bound and unbound forms) may leak from the vascular space (this is the basis for Miles assays, variations of which are used as a (limited) measure of vascular permeability [109]). It was appreciated by the 1950's that a major contribution to the discrepancy between large vessel and whole body hematocrit was made by the differing velocities of red cells and plasma particularly as blood flows through microvessels. Thus, the large vessel hematocrit, H_{LV}, is the ratio of the flow of red cells to the flow of blood through the circulation (see Revised Starling Chap. 2). The flow of cells, Fc, or plasma, Fp, through the circulation of an organ or tissue can be thought of as the volume of cells divided by the mean transit time of the cells, t_c, through the vessels. Similarly the flow of plasma is equal to the volume of plasma Vp divided by its mean transit time, t_p. Measurements of the mean transit times of labelled red cells and plasma show considerable variation from organ to organ and from time to time in the same organ. While reported measurements of the ratio of *tc/tp* through the pulmonary circulation are in the range of 0.98–0.99, the ratio for the liver is closer to 0.5 [110]. If plasma volume is estimated from red cell volume and large vessel hematocrit, then since:

$$H_{LV}/100 = Fc/(Fc+Fp) = 1/(1+Fp/Fc) = 1/\left[1+(Vp/Vc)\cdot(tc/tp)\right] \text{ and } Vp = Vc(tp/tc)\left[(100/H_{LV})-1\right] \tag{3.5}$$

If the whole body hematocrit were substituted for H_{LV}, the term tp/tc would not be part of the expression. Rehm et al. and Jacobs et al. minimise the errors introduced by assuming tp/tc = 1 by using the hematocrit of arterial blood [105, 106]. Providing the fractions of cells and plasma in the blood of the right ventricle approximate to the ratio of their total volumes and the ratio *tc/tp* through the pulmonary circulation remains close to one, considerable error may be avoided. If hematocrit is determined from the venous blood however, fluctuations in tc/tp through peripheral circulatory beds may suggest several 100 ml of fluid entering or leaving the plasma.

Perhaps the most serious misunderstanding of the Rehm et al. and Jacob et al. interpretation is the failure to recognize that the non-circulating component of

plasma represents a virtual volume, not a real one. Changes in its value represent changes in the amount of tracer that is attached to circulating plasma proteins. If m is the amount of tracer injected into the circulation and m_b is the amount of tracer that is bound within the glycocalyx, eq. (3.4) can be extended as:

$$m / Cp = Vp + \lambda Vg + m_b / Cp \tag{3.6}$$

If the affinity of the binding sites for tracer within the glycocalyx is greater than the affinity of plasma proteins for tracer, the ratio of m_b/m may increase as Cp falls as circulating tracer is removed by the liver. This could be mistaken for an increase in the non-circulating component of plasma volume. Alternatively, if repeated estimates of plasma volume are made, the failure of tracer to dissociate from a fraction of its binding sites in the glycocalyx could be incorrectly interpreted as a decrease in glycocalyx volume and an expansion of plasma volume.eh.

It is also noted that in a detailed review of the ways that the new understanding of the fluid exchange through the glycocalyx helps clinicians to evaluate fluid therapy, Woodcock and Woodcock [14] also include in discussion the idea that fluid therapies change the amount of the plasma volume that is trapped in the glycocalyx (see Chap. 2 on Revised Starling Principle for details.). This idea needs much further evaluation because the amount of plasma trapped in the glycocalyx may not be as large as the current measurements of glycocalyx volume suggest.

The foregoing reflects the authors' critical view of whole body glycocalyx volume measurements, which, we hope, will draw attention to the difficulties of measuring and interpreting plasma volume (and particularly changes in plasma volume) using dilution techniques. As noted at the beginning of this section, the principle is simple but meeting the conditions under which it can be rigorously applied are not.

The Glycocalyx in Large Vessels

It is noted that estimates of glycocalyx volume of the order of 0.7 to more than 1.5 L imply a glycocalyx thickness, averaged over the surface area of the human vasculature of 2–3 μm (assuming surface area of 350 m^2 [75]). Part of the confidence in the side stream imaging method and glycocalyx volume estimates is that some measurement of glycocalyx thickness in larger blood vessel approaches these values. For example in a follow-up to EM studies suggesting the glycocalyx was thinner in areas of the carotid artery in mice that were known to be more susceptible to arteriosclerosis, Van der Berg et al. reported an ESL thickness of 4.3 μm in the common carotid region and 2.2 ± 0.7 μm in the sinus region [111]. In addition to lending support to the hypothesis that thinning of the glycocalyx might be a pre-condition for the development of atherosclerosis, these and related measurements using two photon microscopy [112] and FITC-Dextran exclusion [113] have led to broad acceptance that glycocalyx regions several microns thick may be common in larger vessels. As a step towards further evaluation of such large glycocalyx thickness, it is noted that optical methods are even more difficult to apply in larger vessels with thicker walls than in microvessels such as in Fig. 3.4 and the method used to make

such measurements may bias values. To apply sophisticated imaging in the larger vessels described above (150 μm in diameter) each vessel was dissected, mounted in a perfusion chamber, and perfused with an electrolyte solution containing 0.1% albumin. It is now known (see Section 2 "Composition in Relation to a Layered Structure" SIP and glycocalyx stability) that in mammalian vessels such low albumin concentrations do not maintain S1P concentrations in the range where they stabilize the endothelial barrier and suppress MMP release [47]. Thus at least some glycocalyx components are likely to be disturbed during vessel dissection and perfusion leading to the possibility of a more diffuse, and relatively thick surface layer, similar to those present under inflammatory conditions [17].

Background: Imaging the Glycocalyx: More Detailed Technical Issues

Light vs Electron Microscopy

The theoretical limit for detection of separate objects with light imaging is the diffraction limiting resolution of around 200 nm, but in the wet tissue, near a curved interface this level of resolution is not reached. This means the dimensions of interest for the glycocalyx may often lie below the resolution of light microscopy. Super-resolution light microscopy can, in ideal circumstances, have resolutions circa 30 nm, but as suggested above, this ideal limit is not reached in samples containing the glycocalyx in tissue. It has been used in some cell culture experiments for HS and HA [88]. The indication was that the HA (in cables) was along the membrane underneath the HS, but further investigation in the microvasculature of perfused tissues would be needed to confirm these findings. A further confounder is that antibodies for GAG chains are large and Fab fragments are not yet available making steric exclusion a problem (for all forms of tagged imaging). Electron beams have a wavelength 100,000 times shorter than normal optics and can, in theory, have 100,000 times the resolution of visible light but because electron optics are far less efficient, the resolution is limited currently to 0.05 nm. Below we review additional limitations imposed by the requirement to prepare biological wet biological samples to be processed for sample analysis in a vacuum and to improve contrast by additional staining of selected glycocalyx components [114, 115].

Tissue Preparation

Since the late 1940's, water in biological samples has been replaced with plastic as part of sample preparation. Most biological electron microscopy on tissues is achieved through the following simplified protocol: Fixation with glutaraldehyde; staining/fixation with osmium tetroxide; dehydration with grades of ethanol; replacing the ethanol with a plastic resin; ultra-thin sectioning to obtain sections with about 300 μm sides and 80 nm thickness; and finally staining with uranium acetate.

These are then further stained with more heavy metals and imaged in a transmission electron microscope. These plastic sections give a resin-limited resolution of the order of 0.5–2 nm in the plane of the section and 80 nm in the depth direction.

It is important to emphasize that in transmission electron microscopy the actual substance of interest is not observed, only the material used to stain the objects. The resultant EM images therefore depend on what is preserved to be stained after glutaraldehyde fixation and ethanol washing steps. Sugars, of which proteoglycans are made, do not chemically fix very well and therefore are very often removed during tissue processing. This is one of a number of problems that make the glycocalyx difficult to study. Another is that it resides at an interface where differences between the hardness of resin replacing the vascular contents and the hardness of resin-embedded tissue compromise imaging in electron microscopy.

Advances in Staining Technology

Because of the variety and complexity of the compounds that form when a stain used to enhance contrast binds to a target site, the relation between deposit density and the amount and location of the muco-polysaccharides can be far from straight forward. For example, after accounting for the various oxidation states of ruthenium atoms in the ruthenium-ammonium compound which is the ruthenium red first used to label the glycocalyx, Luft determined that the products seen in electron microscope deposits are the result not only of an initial linking of ruthenium red to acid polysaccharides, but further reactions where the mucopolysaccharide is oxidized and ruthenium red then acts as a catalyst to promote a series of cyclic reactions to successively build up osmium tetroxide-ruthenium red derived compounds in the region. Much more work is needed to understand the complex chemistry of the many additional stains that have been introduced to label the negative charges on the GAG side chains as the binding point. The most common in use is Alcian blue, which in a way is similar to cupromeronic blue, binds relatively selectively to proteoglycans. The advantage of such copper based stains is they can also be seen easily with optical histology helping the selection of areas of interest to section for electron microscopy [116, 117]. Another common stain is lanthanum containing dense highly positively charged ions favoured by the Chappel group and others [118–121]. Other stains from the lanthanoid series of elements have also become cheaper, due to improved purification, including terbium, and combinations such as the Lanthanum/Dysprosium GlycosAminoGlycan adhesion technique (LaDy GAGa) [16, 77]. Also thorium dioxide (an actinoid), a compound previously used for vascular radiography, has been shown recently to give similar patterns of staining of the glycocalyx in the glomerulus to LaDy GAGa [122, 123]. The longer spacings observed between periodic densities are broadly in agreement with previous data. Still, the adage of "correlation does not mean causation" makes it difficult to determine if what is observed is physiological, especially with so few examples and with limited knowledge of the mechanisms of binding and structure preservation. An important area for further research is an understanding of the way the

composition of the glycocalyx, its rate of synthesis and degradation, and its preservation in sections of different thickness are preserved. There may be vast amounts of archived material to re-examine with such new knowledge.

Future Directions in Glycocalyx Imaging

One way to help resolve difficulties of comparing images of the glycocalyx from optical and EM studies is to develop approaches that enable both methods to be applied to the same sample of glycocalyx. For example, fluorescently labeled probes can be used to separately label the endothelial cell membrane and specific components on the glycocalyx before the same tissue is prepared for electron microscopic study. Using this approach, Betteridge and colleagues measured the membrane to outer glycocalyx distance (close to 400 nm) to be similar to the thickness in EM images of the same vessels of the glycocalyx stained with Alcian blue [124], and importantly in this context the optical and electron measurements correlated with each other, hydraulic conductivity and albumin solute permeability.

Biological electron microscopy has broadened, particularly in the last decade. Cryo-electron microscopy makes use of a non-crystalline form of ice formed by very rapidly freezing water to below −135 °C so that a glass-like ice is formed. When applied to studies of protein structure, this has enabled, with modern computing, imaging of molecular structures comparable to x-ray crystallography, but in an aqueous state, the technique winning a Nobel prize in 2017. It is also possible to replace the ice with acetone at around −90 °C and then add a plastic resin. This process should result in far less loss of content than ethanol dehydration and has been attempted, although full interpretation was not clear on the limited samples. Preliminary application of cryo-fixation methods to glycocalyx structure in frog mesentery has yielded some useful results as described in Section "The Glycocalyx as a 3 Dimensional Layered Structure in Microvessels", but other applications (e.g. images that appear to show intracellular material leaking across the endothelial cell membrane as in [125]) have as yet been less satisfactory.

Until recently reconstruction of 3D images of endothelial structures on scales greater than one micron has involved the time consuming process of cutting serial sections for TEM and then manually loading and aligning the area of interest for each section. Separate from the tomographic imaging methods introduced above, 3D scanning electron microscopy gets around this problem by detecting an electron beam's backscattered electrons to build up an image of the surface of a sample. Moreover, once the surface has been imaged, a diamond knife or an ion beam can remove a layer and the new surface imaged. When a diamond knife is used the method is called serial block face scanning electron microscopy and when an ion beam is used the method is called focused ion beam scanning electron microscopy. If additional heavy metals are added, to improve contrast, the images are stunning and resolution can be <10 nm in the plane of the scan and 30 nm in depth for thousands of sections. Preliminary application of this approach to glomerular glycocalyx stained with LaDyGAGa technique showed glycocalyx tufts over the surface of

a glomerular filtration vessel as well as gaps through the glycocalyx to the membrane (See Fig. 3.1) [16]. These images leave many fundamental physiology questions unresolved, but the techniques are available and it is not long before they replace transmission electron microscopy for routine use in plastic sections.

Summary. Frequently Asked Questions and some Answers Based on Sections "Introduction" to "Background: Imaging the Glycocalyx: More Detailed Technical Issues"

The following section summarizes some of the main conclusions in this chapter with a particular focus on questions likely to arise about the role of glycocalyx function and infused fluid composition that effect peri-operative fluid management. Some key issues include:

1. The use of albumin solutions in restoring the glycocalyx during the perioperative period.
2. The role of the glycocalyx when infusion fluids having similar colloid osmotic pressures (COP) are not equally effective in reducing edema formation.
3. Ways to protect the glycocalyx during peri-operative fluid therapy.
4. The role of the glycocalyx in reducing the immune response and coagulation by preventing the adhesion of leukocytes to the endothelium and by binding anticoagulants.
5. The effect of negative charges on the glycocalyx and red cells on the movement of red cells in microvessels and the action of high sodium loads to neutralize those negative charges.
6. Measurement of glycocalyx thickness or volume.

It is important to emphasize that the role of the glycocalyx as a major determinant of the effectiveness of peri-operative fluid therapy has been widely recognized only recently, and it is still early in the process of evaluating the contribution that new insights make to better clinical outcomes. However as explained in this Chapter and the accompanying Chapter on the revised Starling Principle, there are sound arguments derived from a knowledge of glycocalyx and endothelial barrier structure and function that can be applied to guide the clinician in the management of fluid therapy. By far the most important and well understood is the role of the inner glycocalyx as the primary molecular filter, retaining most of the plasma colloids within the vascular volume. This function requires maintenance of the spacing between the fibers of the glycocalyx at dimensions close to the molecular diameters of plasma proteins, particularly albumin. Albumin itself may play a direct role in this organization of the glycocalyx by electrostatic binding that regulates the spacing fibers. Albumin in the circulation and within the glycocalyx also contributes to the delivery of sphingosine-1-phosphate (S1P) stored in red cells to the endothelial cells. S1P acting via the S1P1 receptor regulates signaling pathways that both suppress glycocalyx loss by matrix metalloproteinases, and

stabilizes inter-endothelial cell adhesion mechanisms. However, with respect to the role of albumin containing fluids to restore or maintain the glycocalyx during perioperative fluid therapy (1), it is not clear that addition of albumin to infusion fluids would improve the stability the glycocalyx because albumin concentrations required for glycocalyx stabilization and S1Pdelivery are low. However, it is now recognized that the Apolipoprotein-M fraction of circulating HDLs carries at least 60% of the plasma S1P content. Conditions where Apo-M levels are low may contribute to glycocalyx loss [51].

The first aspect of (2) to consider is the COP of albumin solutions versus saline alone. When the glycocalyx is intact and the capillary pressure in an organ is less than or close to the normal plasma colloid osmotic pressure, infused fluid escapes very slowly into the extravascular space of the organ, avoiding edema (e.g. the lung) because the transvascular hydrostatic pressure difference is always closely balanced by the colloid osmotic pressure difference of plasma proteins across the glycocalyx. This illustrates the application of the Revised Starling Principle as explained in more detail in Chap. 2. Thus in the absence of glycocalyx damage, and any large loss of plasma protein, an effective strategy involving saline infusion sufficient to balance renal and evaporative fluid loss, avoiding over-hydration appears consistent with both clinical observation and current understanding of glycocalyx function. This strategy protects the glycocalyx and guards against edema by avoiding local reperfusion damage due to hypovolemia and poor perfusion on one hand, and dilution of the plasma proteins (hypervolemia) on the other. This conclusion does not apply when plasma protein levels are low and the plasma colloid osmotic pressure is insufficient to maintain the low filtration states indicated above. Then, the effectiveness of albumin in infusion fluid is determined by its contribution to plasma oncotic pressures across the glycocalyx.

Further to the question of the relative effectiveness of albumin containing solution versus alternate colloids in solution (2), present knowledge limits detailed comment. In principle all high molecular weight colloid solutions that are primarily excluded by the glycocalyx should be similarly effective. However, issues arise from observations in animal experiments that an albumin solution may be more effective than a colloid solution containing hydroxyethyl starch (HES) with a higher COP. Leaving aside issues about the relative safety of HES in certain patient populations, it is important to emphasize that macromolecules penetrate the glycocalyx at different rates. In animal model experiments, albumin penetrates the glycocalyx far more slowly than other macromolecules (eg dextran). If the subtle interaction of HES transport by diffusion and coupled water flows leads to HES accumulation in the sub-glycocalyx region, the colloid osmotic pressure difference across the glycocalyx due to infused HES may be much smaller than expected from the COP of the infused fluid. The relative effectiveness of albumin versus other colloids may be modified further when key components of the glycocalyx are lost (as measured by increased plasma composition of heparin sulphate or hyaluronan) causing loss of plasma fluid to the extravascular space because of the trans-vascular leak of plasma macromolecules.

With respect to questions about the restoration of the glycocalyx under conditions where key components are lost (3), the following points can be emphasized: Matrix metalloproteinases are a common mechanism to damage the glycocalyx, so strategies such as the use of MMP inhibitors may be important. Also, because damage to the underlying endothelium (e.g. inflammatory gap formation) disrupts the glycocalyx in the region of intercellular junctions, stabilization of the endothelium (using anti-inflammatory strategies) goes hand-in-hand with glycocalyx stability. On the other hand, alternate actions of HES including the possibility that some high molecular weight components may help plug gaps in the glycocalyx or intercellular gaps under inflammatory conditions cannot be excluded.

With respect to other barrier and binding actions of the glycocalyx that are important during the peri-operative period (4), the idea that the glycocalyx acts as a barrier to leukocyte interaction with the endothelial surface is consistent with known glycocalyx structures forming a deformable mechanical barrier at the endothelial surface. Nevertheless the observation the leukocytes can penetrate closer to the endothelial surface than red cells suggests that other factors such as upregulation of adhesion proteins to increase leukocyte adhesion, and chemokine cofactors, in the inflammatory cascade may be just as important as the mechanical forces in determining leukocyte interactions when the glycocalyx is damaged [126]. Similarly the capacity of the glycocalyx to bind a range of circulating plasma proteins is well established. This includes various plasma components regulating coagulation. The sites for such protein binding are lost or disrupted when the glycocalyx is damaged.

With respect to the contribution of negative charge on the glycocalyx to red cell movement through the smallest microvessels (5), it is noted that under static conditions charge plays an important role in the spacing of the glycocalyx matrix fibers, and it is also important in opposing red cell aggregation, and adhesion of red cells to endothelium. At normal microvascular flow rates, however, red cell movement is dominated by the compressibility of the outer layers of the matrix and resistances to water. This does not rule out more complex electrostatic interactions at very low or intermittent flows, but it is not clear that changes in the glycocalyx under high salt loads can be attributed simply to charge shielding. Recent evidence that salt loading results in sodium accumulation in skin interstitium and that this may play a role in immune responses in the vasculature suggests that high salt loading may modulate vascular structure via an immune response [127].

With respect to biomarkers of glycocalyx function in patients, recent clinical evaluations indicate that increased penetration of red cells into the plasma free layer on the walls of microvessels with microvascular dysfunction but the relative contributions of changes in the glycocalyx and the mechanics of red cell flows independent of the glycocalyx to these measurements remains to be evaluated in different disease states. A recent critical review (Michel et al. [128]) addresses some published misunderstanding of the colloid osmotic pressure difference across the endothelial glycocalyx as a determinant of blood to tissue fluid exchange. Also estimates of infused saline distribution volumes in the vascular space based on volume kinetic analysis [129] are sensitive to the same potential errors in measurements of

hematocrit and Hb concentrations as the estimates of whole body glycocalyx volume described above (see also Chap. 2).

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Techniques for Goal-Directed Fluid Management

4

Paul E. Marik

Abstract

An increasing body of evidence has demonstrated that fluid overload both in the intensive care unit (ICU) and operating room (OR) has a major impact on patient morbidity and mortality. The concept of aggressive fluid resuscitation has evolved into the concept of a physiologic, hemodynamically guided approach to fluid therapy. Fundamental to this approach is the concept of fluid responsiveness, defined as an increase in stroke of at least 10–15% after a mini-fluid bolus. Clinical studies in diverse patient populations have consistently and reproducibly demonstrated that only about 50% of hemodynamically unstable patients are fluid responsive. Traditional clinical signs are unable to predict fluid responsiveness with an acceptable degree of accuracy. The passive leg raising (PLR) maneuver and the fluid bolus test coupled with real-time stroke volume monitoring are the only reliable methods for determining fluid responsiveness. As the hemodynamic response to a fluid challenge is very short lived and large fluid boluses (20–30 ml/kg) are associated with severe volume overload, the fluid bolus (500 ml crystaloid) approach to fluid therapy is recommended.

Key Points

1. Fluid responsiveness is a fundamental concept in the management of hemodynamically unstable patients.
2. Fluid responsiveness is defined as an increase in stroke volume of 10–15% following a fluid challenge.
3. Only about 50% of hemodynamically unstable patients are volume responders.

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4. Traditional clinical signs are unable to predict fluid responsiveness with an acceptable degree of accuracy.
5. The passive leg raising (PLR) maneuver and the fluid challenge test coupled with real-time stroke volume monitoring are the only reliable methods for determining fluid responsiveness.
6. The hemodynamic response to a fluid challenge is very short lived (usually less than an hour).

Introduction

An increasing body of evidence has demonstrated that fluid overload both in the intensive care unit (ICU) and operating room (OR) has a major impact on patient morbidity and mortality [1–3]. The concept that aggressive fluid administration is the cornerstone of resuscitation [4, 5] has been seriously challenged, as the harm of aggressive fluid resuscitation is increasingly being recognized [1, 2]. However, decisions regarding fluid therapy, whether this be in the OR or in the ICU, are among the most challenging tasks that clinicians face on a daily basis. This task is made all the more difficult by four poorly recognized concepts, namely, (1) that only about 50% of hemodynamically unstable patients are volume responders, (2) that traditional clinical signs are unable to predict fluid responsiveness with an acceptable degree of accuracy, (3) that the passive leg raising (PLR) maneuver and the fluid challenge test coupled with real-time stroke volume (SV) monitoring are the only reliable methods for determining fluid responsiveness, and (4) the hemodynamic response to a fluid challenge is very short lived (usually less than an hour) [6, 7]. These four factors play a major role in determining the approach to fluid therapy and will be reviewed in this chapter. The widespread failure to appreciate these concepts is highlighted by two publications in which these concepts were "ignored": The first publication was a "Consensus statement on perioperative hemodynamic monitoring by 12 international experts" with the second publication being a systematic review of "Goal directed fluid therapy" [8, 9].

The Concept of Fluid Responsiveness

Fundamentally, the only reason to give any patient a fluid challenge is to increase their SV; if this does not happen, fluid administration serves no useful purpose and is likely to be harmful [6]. Fluid administration will only increase SV if two conditions are met, namely, (1) that the fluid bolus increases the stressed blood volume causing the mean circulating filling pressure (MCFP) to increase and thereby increasing venous return, and (2) that both ventricles are functioning on the ascending limb of the Frank-Starling curve [10]. The heart can only pump into the arteries that which it receives [11]. Venous return is therefore a major factor determining cardiac output. As approximately 70% of the blood volume is within the venous system, changes in venous blood volume play a major role in determining venous return and cardiac output. The venous system can be divided into two theoretical

compartments: the unstressed and stressed volume [12]. The intravascular volume that fills the venous system to the point where intravascular pressure starts to rise is called "unstressed volume," whereas the volume that stretches the veins and causes intravascular pressure to rise is called the "stressed volume" [12]. The stressed blood volume is the major contributor of venous pressure and venous return. According to Guytonian physiology, the MCFP is conceptualized as the pressure distending the vasculature when the heart is stopped (zero flow) and the pressures in all segments of the circulatory system have equalized [12–15]. The mean MCFP is regarded as the driving pressure that determines venous return and is considered synonymous with the effective circulatory blood volume [12–15]. The mean MCFP in humans is normally in the range of 8–10 mmHg [12–15]. The driving force for venous return is determined by the gradient between the MCFP and the central venous pressure (CVP). An increase in the CVP or a fall in the MCFP will reduce venous return, SV, and cardiac output. Theoretically if the CVP increases to the point that it is equivalent to the MCFP, venous return to the heart falls dramatically and cardiac output approaches zero.

According to the Frank-Starling principle as the preload increases left ventricular SV increases until the optimal preload is achieved at which point the SV remains relatively constant [6]. This concept assumes that both ventricles are operating on similar points of their Frank-Starling curve, as the SV of each ventricle must be equal. In patients with right ventricular (RV) dysfunction, SV may not increase with fluid loading (it may actually decrease) even though the left ventricle (LV) is preload responsive. The adverse effects of fluid loading when a patient is on the flat portion of the Frank-Starling curve are related to the shape of the ventricular pressure-volume curve. As the patient reaches the plateau of his/her Frank-Starling curve atrial pressures increase sharply, increasing venous and pulmonary hydrostatic pressures, causing a shift of fluid into the interstitial space with an increase in pulmonary and tissue edema (see Fig. 4.1) [16]. Furthermore, increased cardiac filling pressures increase the release of natriuretic peptides. Natriuretic peptides cleave membrane-bound proteoglycans and glycoproteins off the endothelial glycocalyx increasing endothelial permeability [17–19]. In addition, increased natriuretic peptides inhibit the lymphatic propulsive motor activity, reducing lymphatic drainage, and further promoting tissue edema [20–22]. Furthermore, increased right atrial pressure (CVP) is transmitted backward, increasing venous pressure in vital organs and impairing microcirculatory flow and organ function [23].

Studies in heterogenous groups of critically ill and injured patients and those undergoing surgery have reproducibly and consistently demonstrated that only about 50% of hemodynamically unstable patients will increase their SV by greater than 10–15% following a fluid bolus (usually 500 cc), a condition known as "fluid responsiveness" [6, 24–27]. This is a fundamental observation of major clinical importance and challenges the concept that fluid administration is the cornerstone of resuscitation of hemodynamically unstable patients. This observation implies that approximately 50% of hemodynamically unstable patients in the emergency department, ICU, or OR will not respond to a fluid challenge. Furthermore, as demonstrated in Fig. 4.1, as patients "ascend" their Frank-Starling curve, the increase in SV with repeated fluid boluses diminishes while the adverse effects of fluid loading

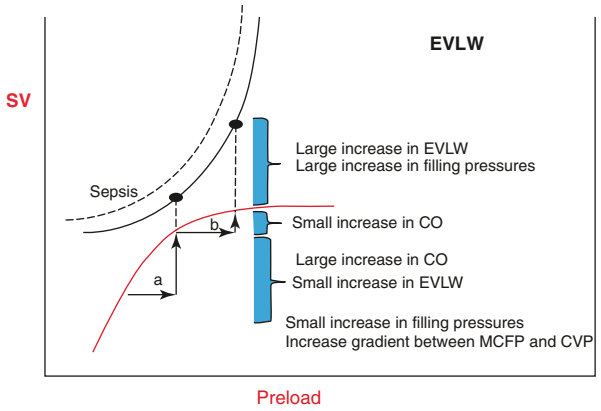

Fig. 4.1 Superimposition of the Frank-Starling and Marik-Phillips curves demonstrating the effects of increasing preload on stroke volume and lung water in a patient who is preload responsive (**a**) and nonresponsive (**b**). With sepsis the EVLW curve is shifted to the left. *EVLW* extravascular lung water, *CO* cardiac output, *MCFP* mean circulating filling pressure, *SV* stroke volume (Reproduced with permission from Marik and Lemson [16])

increase (diminishing returns as the plateau of the Frank-Starling curve is reached). These observations suggest that determining whether a patient is fluid responsive as well as determining the patient's "position" on his/her Frank-Starling curve should be determined prior to each fluid bolus. Unless the fluid bolus results in a significant increase in SV, it serves no useful purpose and is likely to be harmful. Furthermore, it is likely that the patients' clinical diagnosis, the presence of underlying cardiac disease, and the clinical setting will influence the percentage of patients who are fluid responders. Due to the effects of sepsis on the venous capacitance vessels and myocardial function, it is likely that less than 40% of hypotensive patients with severe sepsis or septic shock are fluid responders [28–30]. It should be noted that diastolic dysfunction appears to be at least twice as common as systolic dysfunction in patients with sepsis [31, 32], and this significantly limits preload responsiveness. This concept was highlighted by a landmark study published by Ognibene et al. in 1988 who reported an insignificant increase LV stroke work index and LV end-diastolic volume index in patients with septic shock who received a fluid challenge [33]. It must also be emphasized that fluid responsiveness only occurs in patients with biventricular preload responsiveness. Patients with significant RV dysfunction may not respond to a fluid bolus despite the fact that the LV has preload response.

Methods to Assess Fluid Responsiveness

Physical examination, chest radiography, and urine output (particularly in septic patients) have limited value in guiding fluid management [24, 34–37]. It is therefore quite curious that the Surviving Sepsis Campaign Guidelines recommend "Repeat focused exam by a licensed independent practitioner including vital signs,

Table 4.1 Techniques for assessing fluid responsiveness

Static pressure and volume parameters (ROC ~ 0.5–0.6)
Central venous pressure (CVP)
Pulmonary artery occlusion pressure (PAOP)
Inferior vena cava (IVC) diameter
Flow corrected time (FTc)
Right ventricular end-diastolic volume (RVEDV)
Left ventricular end-diastolic volume (LVEDV)
IVC distensibility index (dIVC)
Dynamic techniques based on heart-lung interactions (ROC ~ 0.6–0.8)
Pulse pressure variation (PPV)
Stroke volume variation (SVV)
Pleth variability index (PVI)
Carotid Doppler blood flow variation (ROC ~0.9)
Techniques based on real or virtual fluid challenge (ROC ~ 0.9)
Passive leg raising (PLR)
Fluid challenge (350–500 cc)

ROC area under receiver operator characteristic curve

cardiopulmonary, capillary refill, pulse, and skin findings" to assess volume status [34]. It needs to be stressed that physical examination cannot be used to predict fluid responsiveness and physical examination is unreliable for estimating intravascular volume status [24, 34–37]. As it is now widely accepted that bedside clinical examination and vital signs have very limited utility in assessing a patient's fluid status, hemodynamic parameters have been used for predicting fluid responsiveness. With increased understanding of the physiologic principles underlying fluid responsiveness and an improvement in monitoring technology, the hemodynamic parameters used to assess fluid responsiveness have evolved over time [16]. Initially static pressure variables including the CVP and pulmonary artery occlusion pressure (PAOP) were used to guide fluid therapy, followed by dynamic changes in pressure and flow variables in response to changes in intrathoracic pressure with mechanical ventilation to changes in flow (SV) following a "virtual" or actual fluid challenge. As will be expanded further in this chapter, these latter two methods are the only techniques that can predict fluid responsiveness with any degree of accuracy; all other techniques should be abandoned as the primary method to determine fluid responsiveness. The hierarchy of hemodynamic methods to determine fluid responsiveness, together with the estimated accuracy of these techniques (as determined by receiver operator characteristics), is listed in Table 4.1.

Static Pressure and Volume Variables for Assessing Fluid Responsiveness

After Hughes and Magovern described the technique of CVP monitoring in 1959, this method became a standard tool for guiding fluid therapy [38]. Over the next two decades clinical studies demonstrated that the CVP was highly inaccurate for

assessing volume status and guiding fluid therapy [39–41]. As we advanced into the current millennium, clinical studies have clearly established that there is a very poor relationship between the CVP and intravascular volume status and that the CVP is unable to predict fluid responsiveness with any degree of accuracy [24, 25, 42]. There is only one study in the entire world literature that has demonstrated a relationship between the CVP and volume status; this study was performed in seven standing mares [43]! The mean area under the receiver operator characteristic (ROC) curve of the CVP for predicting fluid responsiveness is 0.56 (95% CI 0.52–0.60) [24]. It should be noted that a perfect test will have an area under curve (AUC) of 1.0, while a completely useless test has an AUC of 0.5. For a diagnostic test to be of clinical utility the lower limit of the 95% confidence interval (CI) should be above 0.7 [44, 45]. This data demonstrates that the CVP is a "completely useless test" to asses fluid responsiveness and must be abandoned for this purpose. From a physiologic point of view it is difficult to understand how the pressure in the right atrium has any bearing on fluid responsiveness. According to *Kaplan's Cardiac Anesthesia* there are seven flawed assumptions in assuming that the CVP could predict fluid responsiveness [46]. Despite the fact that the CVP should not be used to guide fluid management and that targeting a CVP > 10 mmHg is associated with worse patient outcomes (i.e., death) [1, 47], the CVP continues to be widely used [48] and is currently recommended by major anesthesia textbooks [49] and by the Surviving Sepsis Campaign [34]. A recent consensus statement by 12 international experts in the field of hemodynamic monitoring state that "when the CVP is low (<6 mmHg) with a concomitant low cardiac output, there is almost certainly some degree of hypovolemia" [8]. Furthermore, this document suggests that the CVP "can be used to assess the dynamic response to a fluid challenge" (see below). These statements are incorrect, are unsupported by the literature, reflect a lack of understanding of cardiovascular physiology, and perpetuate the myths associated with CVP monitoring [24, 42, 50]. Cannesson et al. surveyed anesthesiologists in North America and Europe regarding techniques of perioperative hemodynamic monitoring [51]. In this study the CVP was the most common monitoring technique reported (after measurement of the blood pressure), with 72% of American and 83% of European anesthesiologists using this technique. It is important to emphasize that a normal CVP is between 0 and 2 mmHg; this is necessary to ensure adequate venous return and cardiac output (venous return = MCFP − CVP). Clinicians seem compelled to give fluid when the CVP is less than 8 mmHg; the only solution to this pervasive problem is to stop measuring the CVP.

The change in the CVP following a fluid challenge is frequently used to guide further fluid management. This strategy was described several decades ago by Weil and Henning who proposed the 2–5 CVP Rule [52]. According to this scheme, the CVP is measured at 10 min intervals following a fluid challenge. If the change in CVP is <2 mmHg the infusion is continued, if it is between 2 and 5 mmHg the infusion is interrupted and reevaluated after a 10 min wait, while if the change is >5 mmHg the infusion is stopped [52, 53]. However the 2–5 CVP rule or the change in the CVP after a fluid bolus is unable to predict fluid responsiveness [24, 42].

Swan and Ganz developed the flow-directed pulmonary artery catheter (PAC) in 1970 allowing measurement of the PAOP. A commonly cited benefit of PAC is that it provides filling pressures that can be used to identify fluid responsiveness and guide fluid administration. However, these filling pressures have been found to be neither uniformly accurate nor effective for fluid guidance. The PAOP suffers from the same limitations as the CVP [24, 42]. Multiple studies have shown a poor relationship between the PAOP and circulating blood volume, SV, and left ventricular end-diastolic volume [54–59]. Furthermore, the PAOP is unable to predict fluid responsiveness [6, 50, 60]. Like the CVP, the PAOP should not be used to guide fluid management.

Transesophageal echocardiography (TEE) (transgastric, mid-papillary short axis view) has been used to assess left ventricular dimensions in patients undergoing mechanical ventilation. The left ventricular end-diastolic area (LVEDA) has been shown to correlate well with the intrathoracic blood volume (ITBV) and global end-diastolic volume (GEDV) as measured by transpulmonary thermodilution [61, 62], as well as with LV end-diastolic volume as measured by scintography [63–65]. An end-diastolic diameter of <25 mm and a LVEDA of <55 cm^2 have been used to diagnose hypovolemia [66]. However, the LVEDA does not appear to be a good predictor of fluid responsiveness [67–72]. It should be recognized that a small LVEDA does not always reflect decreased intravascular volume. Small LV volumes can be seen with restriction to filling due to decreased ventricular compliance (hypertrophy, ischemia), acute cor pulmonale (acute RV dysfunction), and pericardial disease. Therefore, while the LVEDA may be a good measure of preload, preload does not necessarily translate into preload responsiveness. Similarly, while the ITBV and GEDV provide an estimate of intravascular volume and preload, it has the same limitations as the LVEDA in predicting volume responsiveness [70, 73, 74].

"Dynamic" Methods to Assess Fluid Responsiveness

Following the "widespread" recognition that the CVP/PAOP has no utility in guiding fluid resuscitation [60], the idea that heart-lung interactions during mechanical ventilation could be used to predict fluid responsiveness was championed by Michard, Pinsky, Teboul, and others in the early 2000s [67, 75]. The principles underling this technique are based on simple physiology (see Fig. 4.2) [6, 76]. Intermittent positive-pressure ventilation induces cyclic changes in the loading conditions of the left and right ventricles. Increased intrathoracic pressure during inspiration decreases venous return and increases afterload of the right ventricle [6]. The reduction in RV preload and increase in RV afterload both lead to a decrease in RV stroke volume, which is at a minimum at the end of the inspiratory period. The inspiratory reduction in RV stroke volume leads to a decrease in LV filling after a phase lag of two or three heart beats. Consequently there is a cyclic decrease in the pulse pressure and stroke volume immediately following a positive-pressure breath. These cyclic changes in stroke volume and pulse pressure are greater when the ventricles operate on the steep rather than the flat portion of the Frank-Starling curve [6,

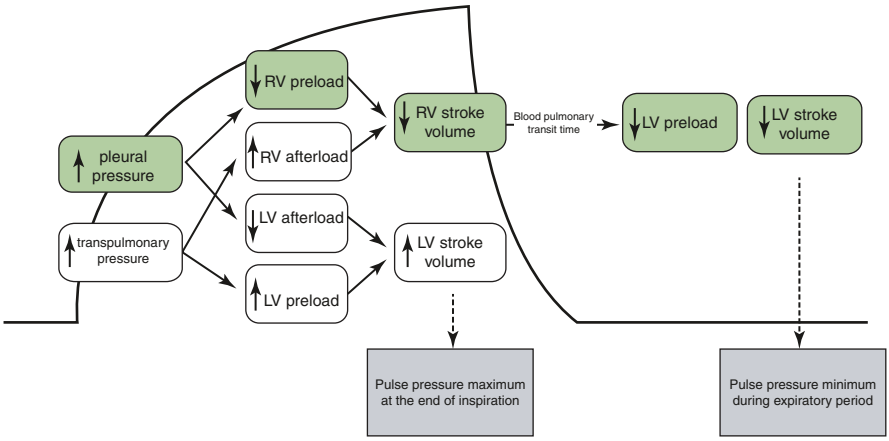

Fig. 4.2 Heart-lung interactions during mechanical ventilation to assess volume status. The cyclic changes in left ventricular (*LV*) stroke volume are mainly related to the expiratory decrease in LV preload due to the inspiratory decrease in right ventricular (*RV*) filling

76]. The pulse pressure variation (PPV) (or stroke volume variation) is calculated using the following formula:

$$\Delta\left(\text{Delta}\right)\text{PP} = 100 \times \left(\text{PP}_{\max} - \text{PP}_{\min}\right) / \left[\left(\text{PP}_{\max} + \text{PP}_{\min}\right) / 2\right]$$

A pulse pressure variation (PPV) or stroke volume variation (SVV) of greater than 13% associated with positive-pressure ventilation (volume-controlled ventilation with a tidal volume > 8 ml/kg/IBW) was shown to be predictive of fluid responsiveness [67, 75]. In a meta-analysis published in 2009, it was demonstrated that the PPV was highly predictive of fluid responsiveness (ROC of 0.94; 95% CI 0.93–0.95) [25]. Due to its sound physiological basis, good predictive ability, and apparent simplicity, this technique was met with great enthusiasm and algorithms based on this principle were developed for use in the OR and ICU [77, 78]. However, what was not fully appreciated when the meta-analysis was published was that almost all the studies were performed in a highly controlled environment (usually the OR) and in highly select groups of patients [25]. In a cohort of cardiac surgical patients, Lansdorp and colleagues demonstrated that PPV/SVV was unable to predict volume responsiveness in routine clinical practice [79]. Multiple studies have now confirmed these findings [26, 29, 80–82]. It soon became apparent that a large number of clinical factors interact to limit the accuracy of the PPV/SVV in predicting fluid responsiveness [83, 84]. The conditions that need to be met (all) to ensure accuracy of PPV/SVV include:

- Sinus rhythm
- Volume cycled ventilation with tidal volume of at least 8 ml/kg ideal body weight
- No ventilator-patient dyssynchrony and no spontaneous breathing
- Heart rate/respiratory rate ratio > 3.6

- Normal chest wall compliance
- No evidence of cor pulmonale-pulmonary hypertension
- Normal intra-abdominal pressure

Canneson et al. assessed the accuracy of PPV for predicting fluid responsiveness using the "gray zone" approach in 416 patients during general anesthesia and mechanical ventilation [27]. The gray zone approach has been proposed to avoid the binary constraint of a "black-or-white" decision of the ROC curve approach that often does not fit the reality of clinical practice [27]. In this study, 51% of patients were fluid responders. The gray zone approach identified a range of PPV values between 9 and 13% for which fluid responsiveness could not be predicted, with 25% of patients being in the gray zone. This suggests that the PPV may only be useful in predicting fluid responsiveness in patients with either a small (<9%) or large (>13%) PPV. For patients in the gray zone, an alternative method of predicting fluid responsiveness should be used (the fluid challenge technique). It should be noted that in the study by Canneson et al., the average tidal volume was 7.9 ml/kg IBW, with 51% of patients being ventilated with a tidal volume of 8 ml/kg or more. The accuracy of PPV is significantly lower in patients ventilated with a tidal volume of 6 ml/kg, which is now considered the standard of care in both the ICU and OR [83, 85–88]. The accuracy and validity criteria for the use of PPV/SVV in the ICU appear significantly worse than in the OR [80, 81]. In a multicenter, point prevalence study, Mahjoub and colleagues demonstrated that only 2% of ICU patients met the validity criteria for using the PPV to assess fluid responsiveness [89]. Bias and colleagues used the gray zone approach to determine the accuracy of PPV (and CVP) in 556 ICU patients undergoing mechanical ventilation [26]. In order to be included in this study the standard exclusion criteria, except for a tidal volume of <8 mls/kg, were used. In this study a fluid challenge led to an increase in stroke volume ≥ 15% in 48% of patients. The AUC of the ROC curve for PPV and CVP were 0.73 (95% CI; 0.68–0.77) and 0.64 (95% CI; 0.59–0.70), respectively. A gray zone of 4–17% for PPV was found, with 62% of patients being in the gray zone.

The pulse oximeter plethysmographic waveform differs from the arterial pressure waveform by measuring volume rather than pressure changes. Dynamic changes in both the peak and amplitude of the pulse oximeter plethysmographic waveform during mechanical ventilation have been used to predict fluid responsiveness [90]. The changes of the plethysmographic waveform with positive-pressure ventilation have shown a significant correlation with the PPV with an accuracy similar to that of the PPV in predicting fluid responsiveness in various settings [91–93]. The pleth variability index (PVI) is an automated measure of the change in the perfusion index (PI) that occurs during a respiratory cycle (Masimo Corporation, Irvine, CA). The PI is the infrared pulsatile signal indexed against the nonpulsatile signal and reflects the amplitude of the pulse oximeter waveform. The PVI correlates closely with the respiratory-induced variation in the plethysmographic and arterial pressure waveforms [94, 95]. However, the PVI suffers from the same limitations in terms of applicability and accuracy as the PPV. Furthermore, the value of the PVI is limited in patients with a low PI [96]. In patients undergoing major

surgery whose volume status was optimized using esophageal Doppler cardiac output monitoring, Davies et al. reported that the ROC for fluid responsiveness was 0.61 (95% CI, 0.46–0.76) and 0.59 (95% CI, 0.46–0.71) for PPV and PVI respectively [97]. Yokose et al. reported that the PI and PVI were unable to predict maternal hypotension in spontaneously breathing patients undergoing elective caesarian delivery performed under spinal anesthesia [98].

These data suggest that due to the limited diagnostic accuracy and the frequency of confounding factors, the PPV/SVV/PVI should not be used as the primary technique for directing fluid management in the OR and ICU. Nevertheless intravascular volume depletion should be suspected in patients who demonstrate marked PPV evident on either an arterial pressure waveform or pulse oximetric waveform. In these situations other tests should be performed to confirm fluid responsiveness. However, as will be noted later, the change in the PPV/SVV following a mini-fluid bolus has been shown to be a good predictor of fluid responsiveness [29].

The inferior vena caval distensibility index (dIVC)—calculated as the ratio of diameter of the inferior vena caval during inspiration (positive pressure) over that during expiration—has become popular and appears to be widely used to determine fluid responsiveness [99]. This approach is based on two small, single-center studies reported by Feissel et al. ($n = 39$) in 2003 and by Barbier et al. ($n = 20$) in 2004, who claimed that the "respiratory change in IVC diameter is an accurate predictor of fluid responsiveness" [100, 101]. It should be noted that in both of these studies a tidal volume of ≥8 ml/kg was used. We have previously reported a ROC of 0.81(95% CI, 0.64–0.99) for the dIVC in predicting fluid responsiveness; our study is limited by the wide confidence interval (with the lower limit below 0.7) and the fact that the mean tidal volume was 8.6 ml/kg [102]. The IVC diameter and its respirophasic variation have been well established to be an indirect measurement of the right atrial pressure (CVP) [103–107]. However, it is now widely recognized that the CVP is worthless for predicting volume status and fluid responsiveness [24, 42]. It would therefore appear illogical that an indirect measure of right atrial pressure (CVP) would predict fluid responsiveness. More recent studies have confirmed this assumption. Ibarra-Estrada and colleagues compared a number of methods for assessing fluid responsiveness in patients undergoing mechanical ventilation with a lung protection strategy (tidal volume of 6 ml/kg IBW) [82]. The ROC for the dIVC and IVC diameter were 0.54 (95% CI, 0.41–0.67) and 0.52 (95% CI, 0.39–0.65), respectively, which were no better than that for the CVP (0.52; 95% CI, 0.38–0.65). The IVC diameter and dIVC have been studied in spontaneously breathing patients. Corl et al. evaluated the role of dIVC in predicting fluid responsiveness in spontaneously breathing emergency department patients [37]. In this study the dIVC was unable to predict fluid responsiveness (ROC of 0.46, 95% CI 0.21–0.71). Additional studies have demonstrated that changes in the IVC diameter and dIVC correlate poorly with changes in hemodynamics following 500 cc of blood loss in healthy volunteers [108, 109]. These studies suggest that the IVC diameter and dIVC should not be used to assess fluid responsiveness in both mechanically ventilated and spontaneously breathing patients.

Echocardiography has been suggested as a method for evaluating fluid responsiveness [110]. However, transthoracic measurements of left ventricular outflow tract velocities (VTI) for the estimation of SV are not easily reproducible or obtainable [82, 111–113]. Transesophageal echocardiography has better diagnostic accuracy; however, this test is invasive and requires clinicians with expertise in this technique [67, 114]. Furthermore, echocardiography is not ideal for detecting rapid changes in SV following a passive leg raising (PLR) maneuver or fluid challenge and for monitoring changes in hemodynamic status. Thus, alternative ultrasonographic methods, including carotid artery and branchial artery velocities, have been examined as surrogates for stroke volume [110, 115]. Measurement of carotid peak flow can be rapidly performed with less difficulty than for other echocardiographic variables. The preferential diversion of blood flow in hemodynamically compromised patients toward the carotid arteries and away from the peripheral arteries suggests that in critically ill patients, the carotid artery may be the preferred site for assessing changes in flow velocities [81].

While the SVV, PPV, and dIVC have limited value in predicting fluid responsiveness, the respiratory variation in carotid Doppler peak velocity (Δ[Delta] CDPV) has been reported to reliably predict fluid responsiveness in mechanically ventilated patients undergoing lung protective ventilation [82]. In the study by Ibarra-Estrada et al., the Δ(Delta) CDPV had the best predictive value of all the parameters studied (ROC 0.88; 95% CI 0.77–0.95), with the ROC for the SVV, PPV, and dIVC being 0.72 (95% CI, 0.59–0.83), 0.63 (95% CI, 0.49–0.75), and 0.54 (95% CI 0.41–0.67), respectively [82]. Similarly, Song et al. demonstrated that the Δ(Delta) CDPV had better predictive value for determining fluid responsiveness in patients undergoing general anesthesia than the PPV [116]. However, it should be noted that in this study patients were ventilated with a tidal volume of 8 ml/kg IBW. We have previously demonstrated that the change in carotid arterial blood flow (as measured by carotid Doppler) was highly predictive of fluid responsiveness in critically ill patients (both vented and spontaneous breathing) following a passive leg raising (PLR) maneuver [81]. Similarly, Luzi et al. reported that change in peak femoral Doppler velocity after a fluid challenge was predictive of fluid responsiveness [117]. The Δ(Delta) CDPV appears to be a useful technique to assess fluid responsiveness in both the ICU and OR; however, this technique is best performed by clinicians who have some experience performing carotid Doppler studies. While echocardiography has limited utility in assessing fluid responsiveness [36], this is an essential bedside tool to assess cardiac function in hemodynamically unstable patients. Echocardiography performed by the emergency department physician, intensivist, and anesthesiologist is particularly helpful (essential) in hemodynamically unstable patients who are not fluid responsive. Echocardiography allows the physician to diagnose RV dysfunction, probable diastolic dysfunction (left ventricular hypertrophy and large left atrium), severe systolic dysfunction, major valvular disease, and pericardial effusion—conditions associated with fluid unresponsiveness [99, 118–121].

The Passive Leg Raising Maneuver and the Fluid Challenge

Currently there are only two techniques that are widely available, practical, easy to perform, and physiologically based that can be used to determine fluid responsiveness with a high degree of accuracy, namely, the PLR maneuver and the fluid challenge [6, 16, 122, 123]. For obvious technical reasons the fluid challenge technique is preferred during anesthesia while the PLR is preferred in the ICU and in the perioperative setting [123]. These techniques are best coupled with minimally invasive or noninvasive cardiac output monitors, which can track changes in SV and cardiac output dynamically and in real time [6]. These monitoring technologies include esophageal Doppler (CardioQ-ODM®, Deltex Medical, Chichester, UK), calibrated pulse contour devices (LiDCO®, LidCO Group, London, UK; PICCO®, Pulsion, Feldkirchen, Germany; EV1000®, Edward Life Sciences, Irvine, CA, USA), the bioreactance cardiac output monitor (NICOM®, Cheetah Medical, Newton, MA, USA) and transcutaneous Doppler ultrasound (USCOM®, Sydney, Australia) [124, 125]. A number of noncalibrated or autocalibrating cardiac output devices are currently available, including the FloTrac/Vigileo (Edwards Life Sciences, Irvine CA, USA), ProAQT/Pulsioflex (Pulsion, Feldkirchen, Germany), LiDCOrapid (LidCO Group, London, UK), and the Pressure Recording Analytical Method (PRAM), which is incorporated into the MostCare device (Vyetech Health, Padua, Italy) [124, 125]. These noncalibrated pulse contour devices require an arterial line with the SV being "calculated" based on the characteristics of the arterial waveform using various propriety formulae. Noncalibrated pulse contour devices are less accurate and less precise with poorer trending ability when compared to calibrated pulse contour devices [124, 125]. The FloTrac/Vigileo system has been the most studied, with an analysis of these studies demonstrating that the device does not have adequate accuracy for clinical use in the ICU or OR [124, 125]. Based on limited data, the same assessment appears to apply to the LiDCOrapid and MostCare devices [126–128]. A limited number of studies suggest that the accuracy, precision, and trending ability of the ProAQT/Pulsioflex system is better than that of the FloTrac/Vigileo system [129, 130], and that the device may be suitable for use in high-risk general surgical patients [131]. A number of finger cuff "hemodynamic monitoring devices" are commercially available that do not require an arterial line. Different devices are currently available, with the Finapress Nova device (Finapress Medical Systems, Amsterdam, Netherlands) providing continuous noninvasive arterial blood pressure while the ClearSight device (Edwards Life Sciences, Irvine CA, USA), previously known as Nexfin, provides an estimate of CO. The ClearSight method is based on the measurement of finger arterial pressure by an inflatable cuff around the middle phalange of the finger. The pulsating finger artery is clamped to a constant volume by applying a varying counter pressure equivalent to the arterial pressure using a built-in photoelectric plethysmograph. The resulting finger arterial pressure waveform is reconstructed into a brachial artery pressure waveform. Cardiac output is calculated by a pulse contour method. While the Finapress and ClearSight devices are able to accurately measure blood pressure, the accuracy of the ClearSight device in measuring cardiac output is poor and this

device cannot be used to measure changes in cardiac output following a therapeutic intervention [132–135]. The pulmonary artery catheter is an obsolete technology of historical interest only, and has limited clinical applicability in modern medicine and should not be used for fluid management [136]. Despite the fact that monitoring SV (or cardiac output) is essential for determining fluid responsiveness, in the study by Canneson et al. only 34% of anesthesiologists monitored SV in patients undergoing high-risk surgery [51]. Furthermore, even those who monitored SV rarely used its value for perioperative optimization, despite the fact that hemodynamic optimization in this setting has been demonstrated to improve patient outcomes [137, 138].

The PLR maneuver is performed by lifting the legs passively from the horizontal position and is associated with the gravitational transfer of blood (about 300 ml) from the lower limbs toward the intrathoracic compartment [123, 139, 140]. Beyond its ease of use, this method has the advantage of reversing its effects once the legs are returned to the horizontal position [123, 141, 142]. Therefore, the PLR maneuver may be considered a reversible "auto-transfusion." The ability of a PLR to serve as a test of preload responsiveness has been confirmed in multiple studies performed in critically ill patients [81, 122, 142–149]. The change in aortic blood flow (measured by esophageal Doppler) during a 45° leg elevation was shown to predict the changes in aortic blood flow produced by a 500 mL fluid challenge even in patients with cardiac arrhythmias and/or spontaneous ventilator triggering—situations where PPV lost its predictive ability [142]. A meta-analysis, which pooled the results of eight studies, confirmed the excellent value of PLR to predict fluid responsiveness in critically ill patients with a global area under the ROC curve of 0.95 (95% CI, 0.92–0.95) [122]. The best way to perform a PLR maneuver to predict volume responsiveness is to elevate the lower limbs to 45° (automatic bed elevation or wedge pillow), while at the same time placing the patient in the supine from a 45° semirecumbent position (see Fig. 4.3) [123]. Starting the PLR maneuver from a total horizontal position may induce an insufficient venous blood shift to significantly elevate cardiac preload [150]. By contrast, starting PLR from a semirecumbent position induces a larger increase in cardiac preload as it induces the shift of venous blood not only from both the legs but also from the abdominal compartment [151]. In should be noted that intra-abdominal hypertension (an intra-abdominal pressure of >16 mmHg) impairs venous return and reduces the ability of PLR to detect fluid responsiveness [152]. Since the maximal hemodynamic effects of PLR occur within the first minute of leg

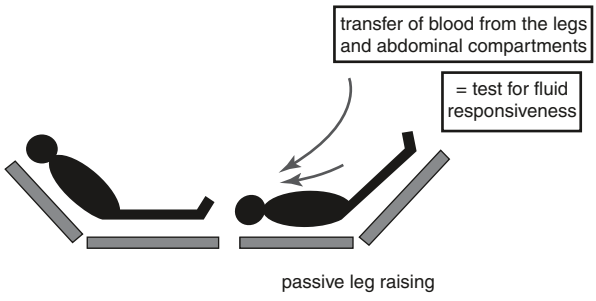

Fig. 4.3 Passive leg raising (PLR) maneuver

Table 4.2 Passive leg raising (PLR) maneuver and fluid challenge in a 72-year-old emaciated male patient with chronic lymphatic leukemia

Time	CI	SVI	Challenge/PLR	Post CI	Post SVI	ΔSVI%
9:20	2.5	20	PLR	2.6	23	9.8
10:10	2.9	24	500 cc fluid challenge	3.9	33	35.4

elevation [123, 142], it is important to assess these effects with a method able to track changes in cardiac output or SV on a real-time basis. It is important to note that the change in blood pressure following a PLR or fluid challenge is a poor guide to fluid responsiveness; SV may increase without a significant change in blood pressure [153]. In approximately 5% of patients the PLR will give a false-negative result. This may occur due to incorrect performance of the technique. In addition, it is likely that thin/emaciated dehydrated patients may have a reduced venous reservoir in their legs due to loss of muscle mass, resulting in an inadequate auto-transfusion with leg raising. In patients with a borderline PLR response or in those patients who are clinically suspected to have intravascular volume depletion despite a negative PLR, a fluid challenge should be performed (see Table 4.2).

The gold standard to determine fluid responsiveness is the change in SV following a fluid challenge [6]. The disadvantage of this technique is that a bolus of fluid is given to a patient who may not benefit. However, the nonresponder should receive no more fluid, and the small volume given should minimize the potential harm. As crystalloids redistribute very rapidly the fluid bolus should be given as quickly as possible and ideally within a 20 min period. A bolus of between 350 and 500 cc is recommended. Fluid boluses in excess of 500 cc are likely to be harmful and are not recommended. Muller et al. reported that a "mini-fluid" challenge with 100 ml colloid over 1 min was highly predictive of fluid responsiveness [154]. Similarly, Wu et al. demonstrated that the change in SV following a 50-ml infusion of crystalloid solution over 10 s was highly predictive of fluid responsiveness [155]. In the study by Wu et al., the mini-fluid bolus was associated with a 17% increase in SV. Mallat reported that change in PPV and SVV following a mini-fluid challenge of 100 ml was highly predictive of fluid responsiveness in patients receiving low-tidal volume ventilation [29]. This may be a useful alternative and/or complementary technique to determine fluid responsiveness in mechanically ventilated patients in the ICU or OR.

Goal-Directed Fluid Management and the Fluid Bolus Approach

The ability of crystalloids to increase intravascular volume is poor. In healthy volunteers only 15% of a crystalloid bolus was reported to remain intravascular at 3 h, with 50% of the infused volume being in the extravascular extracellular compartment [156]. In patients with sepsis it is likely that less than 5% of a crystalloid bolus remains intravascular an hour after the end of the infusion [157, 158]. Nunes et al. assessed the time course of the hemodynamic response of a 500 cc fluid

challenge in patients requiring vasopressor support [159]. In this study, 65% of patients were fluid responders, however the SV increase (in the responders) returned to baseline 60 min after the infusion. Fluid boluses are most frequently given for hypotension or oliguria. While the mean arterial pressure (MAP) may increase immediately following a fluid bolus, this effect is short lived. In a systematic review that investigated the hemodynamic response of fluid boluses in patients with sepsis, Glassford et al. demonstrated that the MAP increased by 7.8 ± 3.8 mmHg immediately following the fluid bolus, by 6.9 ± 2.7 mmHg 30 min following the bolus, and by only 2 mmHg at 1 h, with no increase in the urine output in the hour following the fluid bolus [160]. In order to avoid fluid overload, these data suggest that hemodynamically unstable patients who are fluid responsive should be treated with repeated mini-fluid boluses 350–500 cc) and guided by dynamic changes in their hemodynamic profile (including SV). The normal healthy heart operates on the ascending limb of the Frank-Starling curve and is therefore fluid responsive. The fact that a patient is fluid responsive does not mean that the patient requires a fluid bolus. Only patients with clear evidence of hemodynamic compromise (low stroke volume, hypotension, and tachycardia) and who are fluid responsive should receive a fluid bolus [123]. Furthermore, while an increase of SV of 10% or more is usually considered to indicate fluid responsiveness, there is little data to suggest that such small increases (10–15%) in SV are associated with significant improvements in the patient's hemodynamic status with improved clinical outcomes. It is therefore essential that the risk/benefit ratio be assessed prior to each fluid bolus [123]. Furthermore, not infrequently an alpha agonist may be the preferred intervention in the hypotensive, fluid responsive patient who is vasodilated due to sepsis or anesthesia [161–163]. However, when a fluid bolus is deemed necessary, it is likely that the mini-fluid bolus approach will result in smaller increases in cardiac filling pressures with the attenuated release of atrial natriuretic factors, with less tissue edema, and with a lower cumulative positive fluid balance than large volume fluid resuscitation. Large fluid boluses of 20–30 ml/kg, although still widely recommended [4, 34], are unphysiologic and likely to lead to marked volume overload with severe tissue edema [1, 3]. Tissue edema impairs oxygen and metabolite diffusion, distorts tissue architecture, impedes capillary blood flow and lymphatic drainage and disturbs cell-cell interactions leading to organ dysfunction [164, 165]. In encapsulated organs such as the kidney, tissue edema increases interstitial pressure compromising renal blood flow, which may play a role in etiology of acute kidney injury [166]. Increased extravascular lung water (EVLW) impairs gas exchange, reduces lung compliance, increases the work of breathing, and is a strong independent predictor of death [167, 168].

Conclusion

The methods for assessing fluid responsiveness have evolved from static pressure parameters, which are unable to predict fluid responsiveness, to dynamic indices based on heart-lung interactions during mechanical ventilation, which have a

modest degree of accuracy, to those techniques based on either a virtual or real fluid challenge, which have a high degree of accuracy in predicting fluid responsiveness. Large volume fluid boluses are likely to result in severe volume overload with an increased risk of organ failure. As the hemodynamic response to fluid is short lived, repeated mini-fluid boluses with physiological targets will likely prevent volume overload and its associated morbidities.

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Dynamic Arterial Elastance: Physiology, Data and Implementation

5

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Abstract

Dynamic arterial elastance (Ea_{dyn}) is the reapplication of effective arterial elastance into a practical bedside derivative useful for assessing blood pressure response to various interventions. Typically, the complex interaction of ventricular and arterial systems requires the use of invasive and technically difficult monitors. Now, with the advent of Ea_{dyn} the dynamics of arterial load become available with minimally invasive monitors. Furthermore, the introduction of Ea_{dyn} into current algorithms for perioperative and critical care fluid management has been shown valid and impactful on clinical outcomes.

Key Points

1. Stroke volume variation and pulse pressure variation predict cardiac output responsiveness to intravenous fluid administration, not mean arterial pressure responsiveness.
2. The ratio of pulse pressure variation to stroke volume variation predicts mean arterial pressure responsiveness to intravenous fluid administration and norepinephrine titration.
3. The use of Dynamic Arterial Elastance decreases length of time in the cardiothoracic intensive care unit when employed as part of post-operative management.
4. The generalizability of the clinical utility of Dynamic Arterial Elastance is modest and further study is still needed.

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Introduction

Blood pressure is the potential energy needed to overcome resistive forces in capillary beds and achieve blood flow through tissues. This flow delivers the necessary substrate for energy production, allows immune surveillance, and transfers various ligands and waste products in order to maintain homeostasis. Insufficient flow risks cellular disruption and tissue dysfunction manifesting as pathologic states such as kidney injury, heart failure, liver failure, poor wound healing, and infection. This crucial link between blood pressure and flow emphasizes the need to balance flow with an adequate mean arterial pressure, especially in the operating room and critical care settings.

Interventions employed to achieve a favorable hemodynamic balance are not without risk and prediction of their utility is of great importance to the anesthesiologist. The historic trend has been empiric fluid administration as the mainstay of managing hypotension, but this trend has shifted. It is now recognized that excessive intravascular fluid administration can be detrimental for patients [1]. The use of excessive vasopressor is also problematic. While there are numerous predictive methods of determining the cardiovascular responsiveness to various interventions, the most accurate lack the efficacy for widespread use. Thus, the search for non-invasive, user-friendly methods has progressed.

Two commonly employed methods are stroke volume variation and pulse pressure variation. While useful, these modalities predict increases in cardiac output (CO), not MAP, offering an incomplete assessment of the arterial system [2, 3]. Interestingly, by simply comparing pulse pressure variation (PPV) to stroke volume variation (SVV) a more complete hemodynamic picture emerges. Coined "Dynamic Arterial Elastance," PPV/SVV can predict MAP responsiveness to fluid administration and norepinephrine titration with promising accuracy [4–9].

This chapter explores the physiology of dynamic arterial elastance (Ea_{dyn}) in terms of the influence of arterial system characteristics on arterial waveforms. Subsequently, the chapter examines the clinical evidence followed by a proposed method for implementing dynamic arterial elastance (Ea_{dyn}) into clinical practice.

Arterial Waveforms and the Arterial Tree

Pulse pressure is the transformation of stroke volume to a pressure wave in accordance with arterial system properties. Likewise, the variation of pulse pressure as stroke volume varies is a result of arterial system properties. These primary arterial system properties are effective arterial elastance (Ea) and impedance (Z). Essentially, the degree to which PPV couples with SVV depicts the relative states of effective arterial elastance (Ea) and impedance (Z).

Effective arterial elastance and impedance are the dynamic equivalents of systemic vascular resistance. The static approach, where CO = MAP/SVR, assumes a quasi-steady hemodynamic state, smoothing over the pulsatile nature of the cardiovascular system. Amongst other things, this results in a false depiction of SVR as the sole proportioning factor for the transformation of energy between pressure and flow. This results in an over appreciation of vessel radius in determining pressure and flow dynamics, ignoring arterial tone. By embracing the pulsatility of the cardiovascular

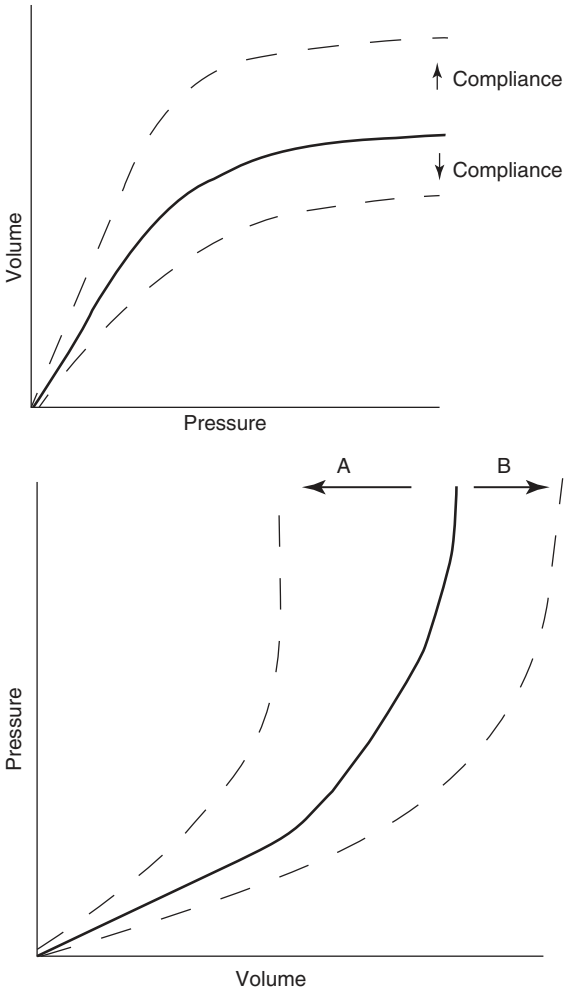

Fig. 5.1 Vascular Compliance curve (Top) and its inverse, Elastance (bottom). The elastance curve may be altered at baseline, for example in atherosclerosis. Elastance also varies by vascular bed and arterial tone. The dashed line depicts the change in the pressure volume relationships for compliance and elastance

system arterial tone becomes a codominant factor. In fact, arterial tone and vessel radius are major elements of both effective arterial elastance (Ea) and impedance (Z).

Effective arterial elastance (Ea) describes the pressure wave of a stroke volume as the result of arterial tone and peripheral vascular resistance in accordance with the 2-element Windkessel model of arterial waveforms. For clarification, elastance is synonymous with tone, and is an intrinsic property of the arterial walls. Its measure is the rate of pressure rise as volume is introduced into an elastic structure. Depicted physiologically, the large central arteries stretch and temporarily store a volumetric portion of a stroke volume. These vessels resist this stretch and attempt to return to their original size, causing a rise in pressure upon systole with subsequent steady decline in pressure as blood discharges to the periphery during diastole. Due to the finite ability of arterial vessels to stretch an increase in total arterial volume results in an exponential increase in rate of pressure rise (See Fig. 5.1). Because PVR controls outflow from the large elastic capacitance vessels it also controls their total volume at a given heart rate and thus effective arterial elastance. The incorporation of PVR into arterial elastance is

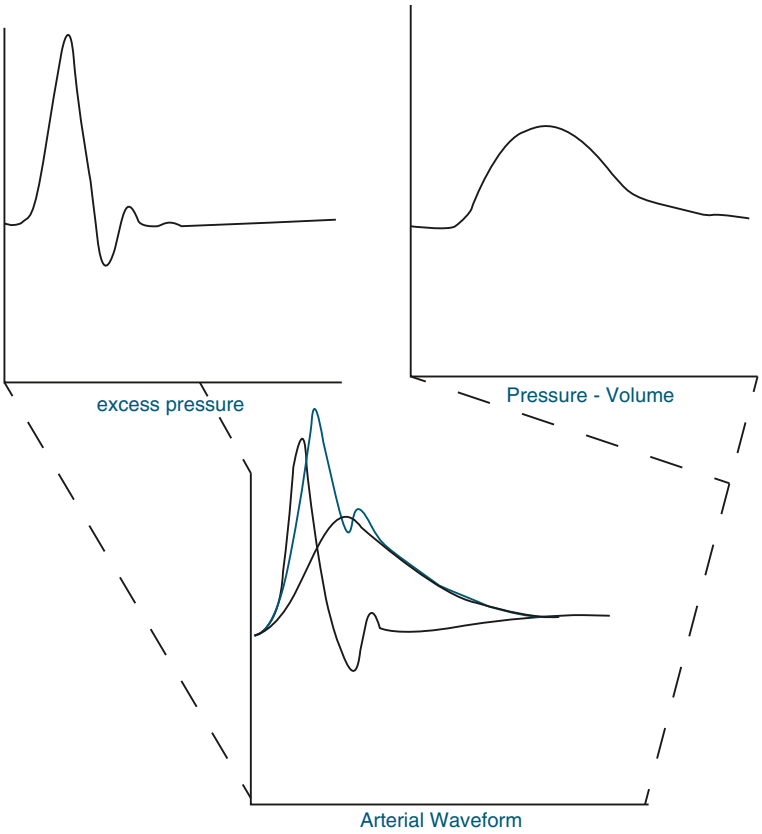

Fig. 5.2 Excess Pressure waveform represented by the Joukowsky equation plus the 2-element Windkessel. The summation illustrates their gross contributions to the arterial waveform. The peak of the pressure volume graph is end systolic pressure, whereas the peak of the arterial waveform summation graph is the systolic pressure

the distinction between arterial elastance as an intrinsic property and effective arterial elastance as an in vivo property. Effective arterial elastance (Ea) is the result of arterial tone (AKA elastance) and peripheral vascular resistance [10–13].

The 2-element Windkessel model uses Ea to accurately predict end systolic pressure and diastolic pressure, but is inaccurate in predicting peak systolic pressure [10] (see Fig. 5.2). The difference between peak systolic pressure and end systolic pressure in the aorta is relatively minor. However, as the pressure wave traverses the arterial system end systolic pressure and peak systolic pressure vary quite drastically [12]. The phenomenon is known as distal pulse pressure amplification and can be attributed to excess pressure (P_{ex}) [14, 15].

Excess pressure (P_{ex}) is the result of reverberation or pressure wave reflection perpendicular to flow beginning and ending in systole. This pressure wave adds to the pressure-volume wave predicted by the 2-element Windkessel in early systole and its effects are negligible by end systole. Excess pressure (P_{ex}) explains the discrepancy between peak systolic pressure and end systolic pressure [15].

The Joukowsky equation elegantly describes how P_{ex} results in peak systolic pressures greater than end systolic pressures. The equation is: dP = QZ, where Q = wave speed, Z = impedance and dP approximates excess pressure (P_{ex}) [16]. Wave speed (Q) is determined by ventricular contractility and arterial elastance. Impedance (Z) is proportional to elastance and SVR. This is all to show P_{ex} increases as elastance, SVR, and contractility increase [16, 17]. As suggested, the phenomenon of distal pulse pressure amplification illustrates the role of excess pressure in stroke volume to pulse pressure transformation and serves as an important example of its role in Ea_{dyn}.

Impedance (Z) increases from the proximal to distal arterial tree because of a change in intrinsic properties of the arterial walls and total caliber of vessel lumen. The main intrinsic property resulting in increased impedance is the increased smooth muscle to elastin ratio in peripheral arteries resulting in increased elastance or intrinsic tone. In addition, the typical taper of total vessel radius near the periphery results in increased SVR. Together the changing arterial properties as the pressure wave traverses the arterial system results in an increase in P_{ex} and thus distal pulse pressure amplifications [15]. The concept is quite obvious when observing arterial waveform tracings at proximal sites versus more distal sites.

Altogether, PPV/SVV describes the relative state of Ea and Z as described by P_{ex} and the 2-element Windkessel. Arterial tone, peripheral vascular resistance, impedance, and LV contractility determine the rate of left ventricular energy dissipated to arterial walls via perpendicular wave reflections (P_{ex}) and vessel wall recoil (Windkessel). The fact that theoretical and experimental data predict a PPV/SVV around 0.8 as the threshold value at which a patient is not likely to respond to a fluid bolus is proof of concept. Furthermore, studies validating PPV/SVV find its predictive capabilities to be independent of SVR. Thus, PPV/SVV offers an assessment of dynamic arterial characteristics beyond the ability of static hemodynamic models.

Combining Joukowsky and Windkessel

Data and Utility

Clinically, the elegance of PPV/SVV is the ability to assess complex hemodynamic characteristics with minimally invasive to potentially non-invasive monitors. Because PPV/SVV is a ratio of change absolute values are not necessary. More specifically, PPV and SVV are derivatives of the Frank Starling curve and PPV/SVV is the derivative of Z and/or Ea curves. This means, theoretically at least, any measure of SVV and PPV would suffice as long as these methods can track change with reasonable accuracy.

Monge et al., one of the first groups to assess the validity of Ea_{dyn}, used two separate methods of measurement in the intensive care unit (ICU). Both study patient populations were mechanically ventilated, preload dependent (by SVV or PPV), without evidence of cardiac pathology. Over half of the patients were septic. Interestingly, there was no difference in hypotensive and normotensive patients in the ability of Ea_{dyn} to predict MAP response of >10% after a 500 mL bolus of NS (Fig. 5.3). Also, over half of the patients received norepinephrine or dopamine infusions, which were

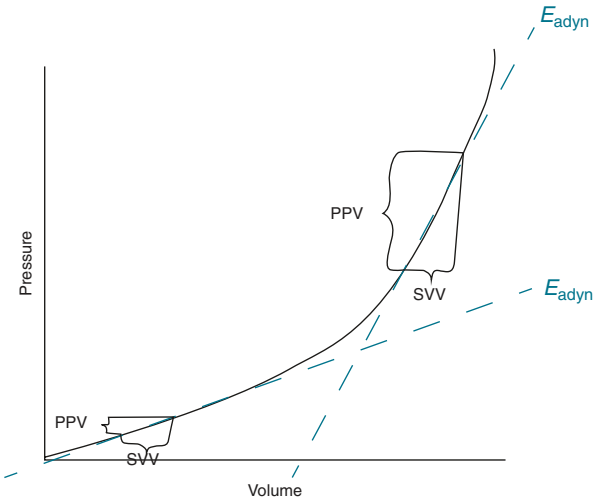

Fig. 5.3 The relationship of pulse pressure variation to stroke volume variation depicts a tangential line along the pressure volume curve of arterial vessels. This relationship can be used to predict the pressure response of the arterial system to an increase in volume

not titrated during the study. Moreover, MAP response continued with repeat boluses until subsequent measure of PPV/SVV decreased. The end result of the two validation studies: PPV/SVV of 0.73 (grey zone 0.72–0.88) predicted MAP increase >10% with a 500 cc bolus of NS with a sensitivity of 90.9% and a specificity of 91.5% [6].

The first validation study by Monge et al. was challenged on the possibility of "mathematical coupling." In this study, the FloTrac/Vigileo platform was used to measure both PPV and SVV from radial arterial line tracings. Because the Vigileo uses waveform characteristics to modify its assessment of stroke volume it was thought the use of the same waveform tracing for both PPV and SVV would erroneously couple the two, invalidating the results of the study [18]. In response, the follow-up study used an esophageal Doppler for SVV and radial arterial waveforms for PPV. The studies had similar results [5, 6].

As with the utilization of different platforms for tracking PPV/SVV, cautious interpretation and implementation is warranted for different patient populations. The Ea value is different in patients with and without hypertensive disease [19]. Pertinent to anesthesia and critical care, a study in cirrhotic patients undergoing liver transplantation did not show Ea_{dyn} to be predictive of MAP response to fluid bolus [20]. Furthermore, Ea_{dyn} was not predictive of pressure response to fluid administration in a study of which >50% of participants were undergoing vascular procedures secondary to atherosclerosis [21]. On a positive note, Ea_{dyn} has been validated in patients undergoing robot assisted laparoscopic prostatectomies [9].

An area of increasing investigation is the use of PPV/SVV to predict MAP responsiveness for the titration of norepinephrine (NE). The end point of three studies showed PPV/SVV to be useful for predicting which patients would have a MAP decrease >10% with an unspecified decrease in NE [4, 7, 8]. Most importantly, one study showed decreased time of NE infusion and time in the ICU when using Ea_{dyn} as part of an algorithm for weaning NE [7]. The cutoff values for predicting MAP decrease with NE decrease are ~0.85–0.90 with a near 100% sensitivity and ~ 70% specificity [4, 7, 8].

As a caveat, the physiology of PPV and SVV coupling has brought with it the debate as to whether or not it is a measure of ventriculo-arterial coupling. Nomenclature aside, based on its physiology, its importance as a measure of arterial system characteristics likely requires normal cardiac and autonomic function [14, 19, 22–24]. Patients with normal cardiac reserve and effective baroreceptor responses will respond harmoniously with changes in arterial load. Whereas patients with alteration in cardiac function, whether it be acute, chronic, and/or pharmacologically induced, the threshold value for prediction may be altered [19, 22–24].

While there is no substitute for clinical judgment, the ratio of PPV/SVV is another tool to help predict hemodynamic status. It is different, although representative of SVR as a dynamic arterial load on stroke volume. Data are limited and suggest unique considerations in certain patient populations warranting further studies before use in these groups (i.e. atherosclerosis, cirrhosis, cardiac dysfunction). Furthermore, different methods of measurement and algorithms may alter validity and optimal predictive values. An understanding of the physiology will help the clinician interpret Ea_{dyn} in a given clinical scenario. Currently, only general recommendations for the clinical implementation of Ea_{dyn} can be provided.

Ea_{dyn} should be used in patients who are expected to or are actively suffering from hypotension to determine the role of vasopressors and/or fluid administration. Cardiac variables should be considered if Ea_{dyn} is below threshold and a patient is not fluid responsive by PPV or SVV.

Recommendations can be made in the setting of hypotension or anticipated hypotension for patients not receiving pharmacologic hemodynamic support. Vasopressors and/or inotropes should be administered prior to or in lieu of giving a fluid bolus to patients who are below the pressure responsiveness threshold. Fluids should be administered if Ea_{dyn} is predictive of a pressure response to a fluid bolus and Ea_{dyn} reassessed. If Ea_{dyn} remains above threshold after a fluid bolus the patient may warrant an additional bolus of fluid. If Ea_{dyn} decreases below threshold after a fluid bolus the patient is likely no longer pressure responsive to fluids, and therefore vasopressors or inotropes should be considered if hypotension persists.

Patients receiving norepinephrine infusion with Ea_{dyn} below threshold should continue norepinephrine with further investigation into the etiology for vasoplegia. Norepinephrine should be decreased if Ea_{dyn} is above a threshold, though the decrement has yet to be empirically determined. The use of Ea_{dyn} for the titration of norepinephrine is the only clinically positive outcome associated with Ea_{dyn} [7].

A challenging area of Ea_{dyn} interpretation is the scenario of preload dependence by SVV or PPV with an Ea_{dyn} below threshold. Pharmacologic support should be given but administration of a fluid bolus is unclear. There are two potential paths as Ea_{dyn} reaches threshold following vasopressor administration: 1. either the patient remains hypotensive, or 2. the MAP goal is achieved. If Ea_{dyn} reaches threshold while titrating pharmacologic support, yet the patient remains hypotensive a fluid bolus should be given. In the patient who achieves MAP goals after pharmacologic support the clinician should question whether or not flow is being sacrificed for pressure. A fluid bolus should be considered when Ea_{dyn} is above threshold in a preload responsive patient receiving vasopressor/inotropic support in an attempt to

wean pharmacologic support. Aside from norepinephrine, there are currently no studies examining the effect of vasopressors/inotropes on Ea_{dyn}. Therefore, the validity of Ea_{dyn} and/or its threshold value may be altered when interpreting in the setting of vasopressors/inotropes other than norepinephrine.

The many caveats to the day-to-day use of Ea_{dyn} warrant a reminder of the physiology of Ea_{dyn}. Its role in hemodynamic assessment is as an indicator of dynamic systemic vascular resistance. As with all clinical tools an understanding of its physiology should guide its bedside implementation.

Conclusion

Ea_{dyn} adds a unique tool to the clinician's armamentarium for the assessment of hemodynamic status. The pulse pressure varies according to stroke volume variation as the result of Z and Ea. Studies validating Ea_{dyn} are promising in predicting pressure responsiveness to fluid bolus and norepinephrine titration. The use of Ea_{dyn} for decreasing norepinephrine use is associated with a decreased length of ICU stay and should be considered for this purpose. Further studies on outcomes in various populations need to be conducted. There may be a role for Ea_{dyn} in Enhanced Recovery After Surgery protocols with cautious interpretation based upon patient characteristics and clinical circumstances. Clinicians should start tracking Ea_{dyn} in practice to further assess the validity and outcomes associated with its use.

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6 The Perioperative Use of Echocardiography for Fluid Management

Maged Argalious

Abstract

This chapter will discuss some common "static" echocardiographic measurements that can guide fluid management including echocardiographic quantification of ventricle dimensions, areas, and volumes. The chapter will mainly focus on "dynamic" echocardiographic measurements of fluid responsiveness that can guide the perioperative physician in the fluid management of patients in the operating room, the postanesthesia care unit (PACU), and in the critical care unit. These include echocardiographic quantification of inferior vena cava and superior vena cava diameters and collapsibility index to guide fluid therapy. In addition, Doppler ultrasound guided approaches to quantification of stroke volume changes both in mechanically ventilated patients (using respiratory-induced changes) and in spontaneously breathing patients (using the passive leg raising test) will be described.

Key Points

1. Echocardiography can be used as a monitoring tool for fluid management if after a diagnostic assessment, repetitive hemodynamic, or anatomic assessments are being made over a period of minutes, hours, or days in the same patient to guide management.
2. Echocardiographic "static" parameters such as left ventricle end systolic and end-diastolic areas and volume are helpful in differentiating the different mechanisms of shock but are not helpful in predicting fluid responsiveness.
3. Echocardiographic "dynamic" measures of fluid responsiveness including IVC and SVC collapsibility index and respiratory variations in left and right ventricle

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stroke volume can be used to predict the response to fluid loading in mechanically ventilated patients before an actual fluid bolus is given and is therefore an essential component of goal-directed fluid therapy. Prediction of fluid responsiveness reduces perioperative morbidity associated with overhydration and fluid overload, including pulmonary complications, postoperative ileus, and increased length of stay.

4. Passive leg raising test coupled with echocardiographic measurement of stroke volume variations is the only validated measure for prediction of fluid responsiveness in spontaneously breathing patients.
5. Echocardiographic dynamic measures of fluid responsiveness have several limitations including the different cutoff values for identification of fluid responders as well as their inability to accurately predict fluid responsiveness in patients with heart rhythms other than sinus, in those with right or left ventricle dysfunction, in patients with pulmonary hypertension, as well as in patients with "low" tidal volume mechanical ventilation that reduces the respiratory variations in echocardiographic dynamic parameters. In addition, these echocardiographic measurements require expertise in performance and interpretation of perioperative echocardiography (transthoracic and transesophageal)

Introduction

In the last decade, there has been an increased understanding of the limitations of "static measures" of volume responsiveness in predicting the response to fluid administration.

While perioperative fluid management requires the integration of several clinical data points including, but not limited to, perioperative fluid balance (fluid deficit, estimated blood loss, urine output), hemodynamic data (blood pressure and heart rate), as well as laboratory data such as lactate level, acid base status, and mixed venous oxygen saturation, these data points are insufficient in predicting the response to fluid loading [1].

Most nonechocardiographic-derived static markers of cardiac preload, especially central venous pressure or pulmonary artery occlusion pressure, but even some echocardiographic-derived parameters such as left ventricular end-diastolic dimension and early/late diastolic wave ratio, do not identify fluid responders from nonresponders [2]. While these static markers can identify whether a cardiac chamber is full or empty and may help identify different mechanisms of shock states (which is certainly important), they do not reliably predict the hemodynamic response to a subsequent fluid bolus administration [3–5].

Identifying that the end goal for optimum fluid management is the optimization of stroke volume, cardiac output for optimum oxygen delivery to tissues and vital organs has resulted in the use of more "dynamic" measures of fluid responsiveness that can inform clinicians whether a subsequent fluid bolus will result in an increase in stroke volume [6].

The physiologic benefit of a fluid bolus is based on the Frank-Starling relationship whereby an increase in cardiac preload results in an increased stroke volume and subsequently an increased cardiac output. This concept assumes that a patient's preload is on the steep portion of the Frank-Starling curve. However, there are several curves that rely on stroke volume and cardiac preload, depending on the ventricular function. A given value of cardiac preload can be associated with an increase in stroke volume and the presence of preload reserve in patients with good ventricular function, whereas the same value of preload will not be associated with an increase in stroke volume (no preload reserve) in patients with poor ventricular function. Thus, it is the actual interaction among the three parameters—preload, stroke volume, and cardiac contractility—that determines fluid responsiveness [7].

Whether administration of a fluid bolus will result in an improvement in stroke volume or whether it will precipitate the occurrence of acute pulmonary edema and result in "overhydration" with its associated complications of gut edema, delayed bowel function, cardiorespiratory complications, and worsening morbidity are at the heart of this dilemma. The last decade has therefore witnessed a steady increase in the use of perioperative echocardiography as a means of obtaining real-time "dynamic" measures of fluid responsiveness in a noninvasive fashion [8–10].

This chapter will discuss some common "static" echocardiographic measurements that can guide fluid management, but will mainly focus on "dynamic" echocardiographic measurements of fluid responsiveness that can guide the perioperative physician in the fluid management of patients in the operating room, the postanesthesia care unit (PACU), and in the critical care unit.

Indications for Echocardiography in Assessment of Volume Status

In a recent report from the American Society of Echocardiography titled "Guidelines for the Use of Echocardiography as a Monitor for Therapeutic Intervention in Adults" [10], the authors proposed that echocardiography be used as a monitoring tool if after a diagnostic assessment, repetitive hemodynamic or anatomic assessments are being made over a period of minutes, hours, or days in the same patient to guide management, including fluid management. This recommendation is in response to the increasing use of echocardiography to guide therapeutic interventions by anesthesiologists, intensivists, cardiologists, and trauma physician and several observational trials and review articles [9, 11] that demonstrate the potential role of echocardiography in decision-making for patients undergoing noncardiac surgery.

This report also extends the indications for the use of echoacardiography beyond the 2010 multidisciplinary guidelines published by the American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists [12] that recommended the use of transesophageal echocardiography (TEE) in patients who are undergoing noncardiac surgery and exhibit persistent hypotension or hypoxia despite therapeutic intervention.

Table 6.1 Differentiation of hypovolemia from other disease states by changes in LVID

	Hypovolemia	Low SVR and or high C.O.
LVIDS or LVESA	Decreased	Decreased
LVIDD or LVEDA	Decreased	Normal

Reference ranges for LVIDD are 3.9–5.3 cm in women and 4.2–5.9 cm in men [13]
SVR systemic vascular resistance, *C.O.* cardiac output, *LVEDA* left ventricle end-diastolic area, *LVESA* left ventricle endsystolic area, *LVIDD* left ventricle internal diameter diastole, *LVIDS* left ventricle internal diameter systole

Two-Dimensional Echocardiographic Assessment of Left Ventricle Chamber Dimensions

Serial measurements of cardiac chamber internal diameter and/or area can be helpful in assessment of volume status. While left ventricle chamber measurements are more common, both right ventricle and left ventricle serial measurements have been described. Small left ventricle internal diameter can be indicative of hypovolemia if measured at end-diastole (Table 6.1) [13].

The timing of measurements is of utmost importance, since a small left ventricle internal diameter at end systole can also occur as a result of increased contractile states (high cardiac output causing a hyperdynamic state) or due to reduction in systemic vascular resistance such as in cases of sepsis and anaphylaxis with resultant vasoplegia.

Several views can be used to measure left ventricle internal dimensions: If transthoracic echocardiography is used, the parasternal short axis or long axis are typically utilized, while transesophageal measurements are typically done using the midesophageal 2-chamber view at the mitral valve leaflet tips (Fig. 6.1). Alternatively, the transgastric long axis view can be used. While the transgastric mid short axis view at the level of the papillary muscles can also be utilized, improper alignment can result in erroneous measurements.

M-mode imaging of the LV minor axis utilizing the aforementioned parasternal TTE views (1 cm distal to the mitral valve annulus at the MV valve leaflet tips) or the TEE transgastric midpapillary SAX view (Fig. 6.2) can also be utilized to measure the LV chamber dimensions in systole and diastole [10].

Regardless of the view used, serial measurement of LV dimensions is recommended to monitor the response to fluids.

Two-Dimensional Echocardiography for Assessment of Ventricle End-Diastolic and End Systolic Areas

It is worthwhile noting that while left ventricle cavity obliteration in the transgastric midshort axis view can provide a rapid diagnosis of inadequate LV preload, 20% of cases with systolic cavity obliteration occur due to an increase in ejection fraction (hyperdynamic circulation with high cardiac output states) state or due to a reduction in afterload (sepsis, anaphylaxis with resultant vasoplegia), highlighting the

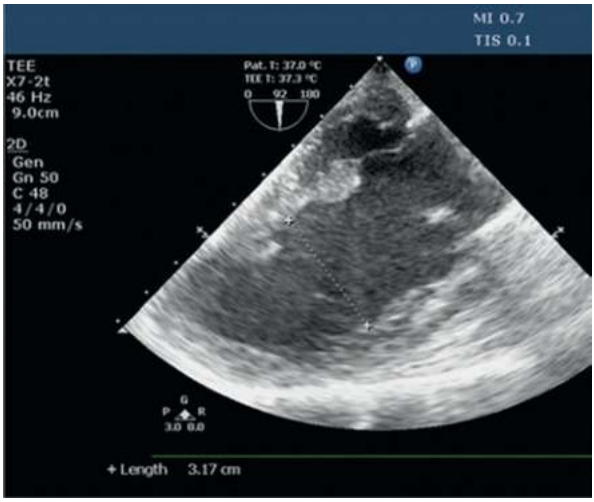

Fig. 6.1 Transesophageal echocardiographic measurements of left ventricular (LV) minor-axis diameter (LVD) from transgastric 2-chamber view of LV, usually best imaged at an angle of approximately 90–110°

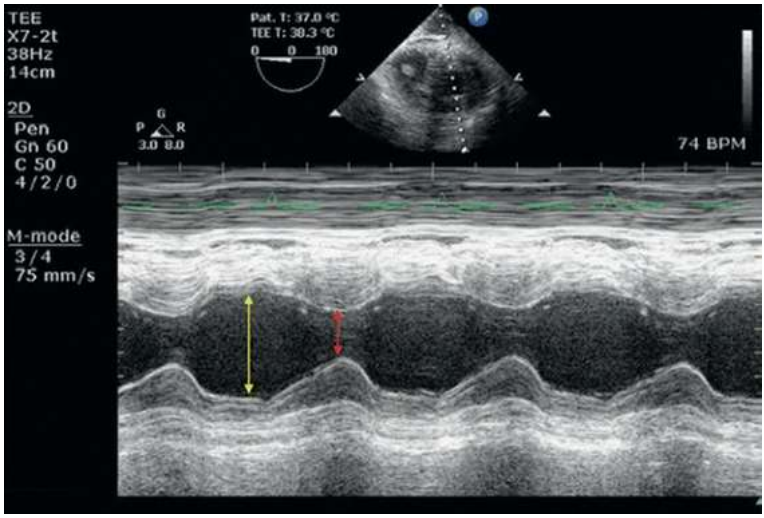

Fig. 6.2 Transesophageal M-mode imaging through the transgastric mid short axis view identifying end-diastolic (*yellow arrow*) and endsystolic (*red arrow*) left ventricle internal diameters

importance of measuring both end-diastolic and endsystolic left ventricle dimensions to differentiate hypovolemia from other conditions (Table 6.1).

Two-Dimensional Echocardiography for Assessment of Left Ventricle Volume

The recommended method for 2-dimensional (2D) echocardiographic volume calculations is the biplane method of disks summation (modified Simpson's rule) [13].

Table 6.2 Normal value ranges for left ventricle volumes in systole and diastole [13]

	Normal LVEDV (LVEDV/BSA)	Normal LVESV (LVESV/BSA)
Women ml (ml/m^2)	56–104 (35–75)	19–49 (12–30)
Men ml (ml/m^2)	67–155 (35–75)	22–58 (12–30)

LVEDV left ventricle end-diastolic volume, *LVESV* left ventricle endsystolic volume, *BSA* body surface area

In transthoracic echocardiography, this is accomplished in the apical 2- and 4-chamber views. In transesophageal echocardiography, the midesophageal 4 chamber (0° on omniplane) and 2 chamber (90° on omniplane) views are used.

Volumetric measurements are usually based on tracings of the interface between the compacted myocardium and the LV cavity in end systole and end-diastole. Table 6.2 identifies normal value ranges for left ventricle volumes in systole and diastole [13]. At the mitral valve level, the contour is closed by connecting the two opposite sections of the mitral ring with a straight line. LV length is defined as the distance between the middle of this line and the most distant point of the LV contour. The advantages of the disk summation method is that it corrects for shape distortion and has less geometric assumptions compared to linear dimension. However, foreshortening of the left ventricle is a frequent problem and can result in volume underestimation. Foreshortening can be reduced by acquiring the views at a reduced depth to focus on the left ventricle cavity. For better delineation and tracing of the left ventricle endocardial border, contrast agents can be injected intravenously [14].

Three-Dimensional Echocardiography for Assessment of Left Ventricle Volume

In patients with good image quality, three-dimensional (3D) echocardiographic measurements are accurate and reproducible [15]. In addition, they do not rely on geometric assumptions and are therefore less prone to foreshortening. 3D image acquisition should therefore focus on including the entire left ventricle within the pyramidal data set [16].

2D and 3D volumetric assessment of left ventricle volume during systole (ESV) and diastole (EDV), in addition to monitoring of fluid status, is most commonly used to calculate ejection fraction using the formula:

$$\mathrm{EF} = \left(\mathrm{EDV} - \mathrm{ESV}\right) / \mathrm{EDV}$$

Inferior Vena Cava Size and Collapsibility

The inferior vena cava (IVC) ends at the floor of the right atrium, just after crossing the diaphragm, and carries about 80% of the venous return to the right atrium. Its route is purely abdominal and is therefore only subject to intra-abdominal pressure [8].

In spontaneously breathing patients, inspiration causes a negative intrathoracic pressure and a subsequent reduction in IVC diameter. This normal inspiratory reduction in IVC diameter is exaggerated in the hypovolemic state. Periodic measurement of IVC diameter and its collapsibility with inspiration has been used to guide fluid management in patients with shock states.

It is important to obtain an appropriate imaging window that maintains the inferior vena cava in view throughout the respiratory cycle, since this facilitates measurement of the IVC size both in inspiration (minimum diameter) and expiration (maximum diameter).

Transthoracic Echocardiography in the Spontaneously Breathing Patient

From subcostal 4-chamber view, the transducer is rotated 90° counterclockwise, always keeping the right atrium on the screen (transducer orientation marker is at 12 o'clock). A depth of 16–24 cm is used, with imaging adjusted to ensure that the merging of the IVC into the right atrium is visualized, thereby confirming that the descending aorta is not erroneously imaged instead (Fig. 6.3).

Both 2D imaging and M-mode imaging can be used to measure IVC diameter and collapsibility. M-mode imaging allows high frame rate measurements of diameter changes that occur throughout the respiratory cycle. The diameter of the IVC should be measured 2–3 cm before it merges with the right atrium. IVC collapsibility index is measured as follows:

$$\text{IVC collapsibility index} = \text{Maximum Diameter IVC}\left(\text{DIVC max}\right) - \text{Minimum Diameter IVC}\left(\text{DIVC min}\right) / \text{Maximum Diameter IVC}\left(\text{DIVC max}\right) \times 100$$

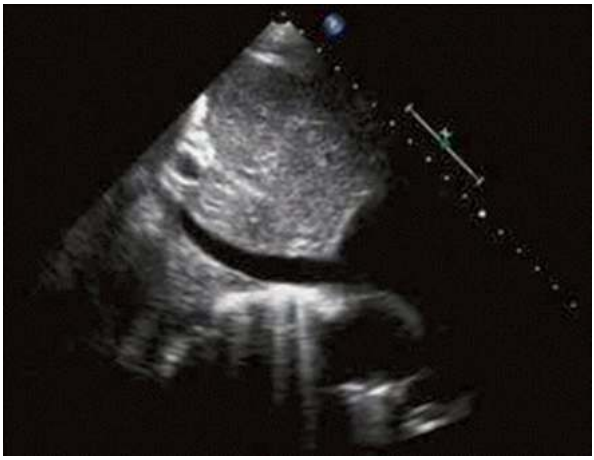

Fig. 6.3 Transthoracic subcostal view of the IVC

Table 6.3 Estimation of right atrial pressure based on IVC diameter and collapsibility with sniff [17]

IVC size (cm)	Collapsibility with sniff (%)	Right atrial pressure (mmHg)
≤2.1	>50	0–5
≤2.1	<50	5–10
>2.1	>50	5–10
>2.1	<50	10–20

Uses of IVC collapsibility index in spontaneously breathing patients:

1. IVC diameter and collapsibility can be used to estimate right atrial pressures (Table 6.3) [17].
2. Assessment of volume status (hypovolemia, hypervolemia).
3. In spontaneously breathing patients, IVC collapsibility index has *not* been validated for assessment of fluid responsiveness.

Transesophageal Echocardiography in the Mechanically Ventilated Patient

Measurement of IVC collapsibility index has also been used in mechanically ventilated septic patients using either transthoracic (TTE as described above) or transesophageal echocardiography (TEE) with 2D and/or M-mode imaging of the IVC.

In TEE, from the midesophageal bicaval view (90–110°), the probe is advanced deeper into the esophagus to bring the IVC to the center of the display, which is followed by multiplane rotation back to 40–70°. On this view, the posterior and anterior walls of the IVC are observed on the top and the bottom of the display, respectively.

The second option to view the IVC starts at the level of the aortic valve at 0°. From this point, the probe is advanced and turned to the right until the tricuspid valve and the coronary sinus come into view. Further advancing and turning to the right will show the IVC and bring it to the center of the display [17].

Uses of IVC collapsibility index in mechanically ventilated patients:

1. Prediction of fluid responsiveness: IVC collapsibility index of 15% and above typically predicts fluid responsiveness [18, 19]
2. Due to its intra-abdominal location, the IVC is *not* suited for estimation of right atrial pressure during mechanical ventilation, especially because positive pressure ventilation causes a dilation of IVC diameter [20, 21]. However, a small IVC diameter (<1.2 cm) has a 100% specificity (with a low sensitivity) for a RA pressure of less than 10 mmHg [22].

Superior Vena Cava Size and Collapsibility

The superior vena cava (SVC) ends at the top of the right atrium. Unlike the IVC, its route is purely intrathoracic. It carries about 20% of the venous return to the right atrium [8].

Transesophageal Echoacardiography in the Mechanically Ventilated Patient

In mechanically ventilated patients, superior vena cava (SVC) collapsibility index has been proposed as a gauge of volume status [23]. Measurements of the SVC will be taken in the midesophageal bicaval view (90–110°) using 2D and/or M-mode echocardiography, 1–2 cm away from the entry point into the right atrium. This technique is analogous to that recommended when measuring IVC diameter and collapsibility [20] and was previously described by Cowie et al. [24] Collapsibility index is defined as maximal SVC diameter during expiration minus minimal diameter during inspiration divided by maximal diameter:

$$\text{SVC collapsibility index} = \text{Maximum Diameter SVC}\left(\text{DSVC max}\right) - \text{Minimum Diameter SVC}\left(\text{DSVC min}\right) / \text{Maximum Diameter SVC}\left(\text{DSVC max}\right) \times 100 \quad \left(\text{Fig. 6.4}\right)$$

A number of 36% allows discrimination between fluid responsive and fluid-unresponsive patients in mechanically ventilated septic patients [23]. Alternatively, a quick qualitative visual approach has been suggested by the same authors [25] to gauge fluid responsiveness based on the presence and degree of SVC collapse. Patients with complete or partial collapse would be considered fluid responsive, while patients with no collapse would be considered fluid nonresponsive (Fig. 6.4):

Major respiratory variation → complete SVC collapse fluid responsive
Moderate respiratory variation → partial SVC collapse fluid responsive
No respiratory variation → no SVC collapse fluid unresponsive

Limitations of the use of respiratory changes in vena caval diameter:

1. In spontaneously breathing patients, respiratory variations of the vena cava cannot be used to predict fluid responsiveness. In these situations, passive leg raising to mimic a fluid bolus (see below) with measurement of left ventricle stroke volume before and after the maneuver is the only described method for assessment of fluid responsiveness in the spontaneously breathing patient.

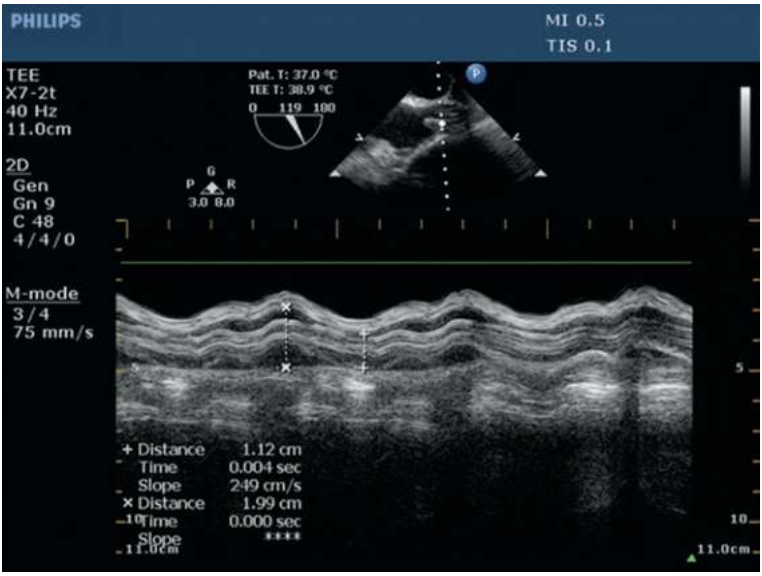

Fig. 6.4 M-mode Assessment of SVC collapsibility index utilizing the TEE midesophageal bicaval view at ~120°. SVC collapsibility index = 1.99 cm − 1.12 cm/1.99 cm × 100 = 43% indicating fluid responsiveness. Note the echogenic density in the SVC representing an indwelling central venous catheter that should not be confused with the wall of the SVC

2. In mechanically ventilated patients, the vena cava diameters and collapsibility cannot be used to estimate right atrial pressure.
3. Fluid responsiveness based on SVC and IVC collapsibility indices has not been validated in patients with rhythms other than sinus rhythms, in those with small tidal volume ventilation (<6 ml/kg) in patients with right or left ventricle dysfunction, or with those with pulmonary hypertension.
4. The cutoff for fluid responsiveness for SVC and IVC collapsibility index vary markedly (around 15% for IVC and 35% for SVC). In addition, the fluid responsiveness cutoff for each one of the vena cava varies across studies, introducing the "gray zone" concept. The gray zone concept of fluid responsiveness refers to patients where the value of the collapsibility index does not definitely determine whether they will or will not be fluid responsive (e.g., a value for IVC collapsibility index between 10 and 15%) [26].

Respiratory Variations in Left Ventricle Stroke Volume

Using transesophageal echocardiography, mechanical ventilation-induced changes in left ventricle stroke volume can be assessed in the deep transgastric 5-chamber view at a transducer angle of 0–20° to align the pulsed wave Doppler signal with the left ventricle outflow tract [8].

The area under the curve of left ventricle flow, also called stroke distance or velocity time integral (VTI) is multiplied by the cross-sectional area of the aortic valve to measure left ventricle stroke volume. (Stroke volume multiplied by the patient's heart rate can then be used to measure the cardiac output.)

Since the cross-sectional area is constant throughout the respiratory cycle, changes in velocity time integral reflect changes in left ventricle stroke volume:

$$\text{Delta}\left(\text{Velocity Time Integral}\right)\ \text{VTI}\ \% = \text{VTI max} - \text{VTI min} \times 100 / \text{VTI mean}$$

where the mean VTI equals the VTI max + VTI min/2 [27].

In hypovolemic patients, the magnitude of respiratory changes that occur with mechanical ventilation exaggerate the difference between the inspiratory and the expiratory left ventricle stroke volume and can be used to assess biventricular preload dependence and fluid responsiveness.

In an attempt to simplify the measurements even further, maximum and minimum peak velocities throughout the respiratory cycle have been used instead of velocity time integrals to measure left ventricle stroke volume changes [22].

While velocity time integral measurements require tracing of the area under the curve of the maximum and minimum VTI area, measuring velocities only requires identification of the maximum and minimum peak velocities throughout the respiratory cycle. Changes in peak velocity can then be calculated as follows:

$$\text{Delta Vpeak}\ (\%) = 100 \times \left(\text{Vpeakmax} - \text{Vpeak min}\right) / \text{Vpeak mean}$$

Where the mean peak velocity equals (Vpeakmax + Vpeakmin)/2.

A Delta Vpeak threshold value of 12% allowed discrimination between responders and nonresponders with a sensitivity of 100% and a specificity of 89% [19] (Fig. 6.5).

The inspiratory phase of positive pressure ventilation causes a reduction in right ventricle stroke volume (through an increase in pleural pressure and transpulmonary pressure) and a concomitant increase in left ventricle stroke volume. In the expiratory phase of positive pressure ventilation, these changes are reversed, with a decrease in left ventricle stroke volume during expiratory phase. These mechanical ventilation-induced changes have also been termed "reverse pulsus paradoxus," since their direction is opposite to those occurring during spontaneous ventilation (whereby the right ventricle stroke volume increases during inspiration and the left ventricle stroke volume decreases during inspiration, with these changes being reversed during spontaneous expiration).

Mechanical ventilation-induced changes of right ventricle stroke volume can also be assessed with pulsed wave Doppler in the right ventricle outflow tract using the midesophageal ascending aorta short axis view at 0–20° on the transducer angle or using the upper esophageal aorta short axis view at 90° with the pulmonary artery outflow in view (Fig. 6.6). This is especially important when transgastric views cannot be obtained for assessment of left ventricle stroke volume changes.

Esophageal Doppler devices introduced through the mouth and adjusted to obtain the highest Doppler velocity signal from the descending aorta have also been

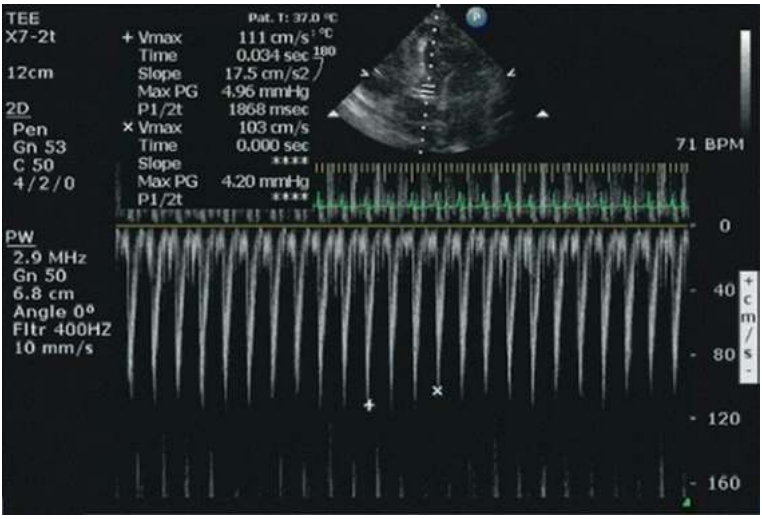

Fig. 6.5 TEE Assessment of Delta V peak in the deep transgastric 5 chamber view. Delta V peak = $111_{cm/s} - 103_{cm/s}/(111_{cm/s} + 103_{cm/s}/2) \times 100 = 7.5\%$ indicating lack of fluid responsiveness

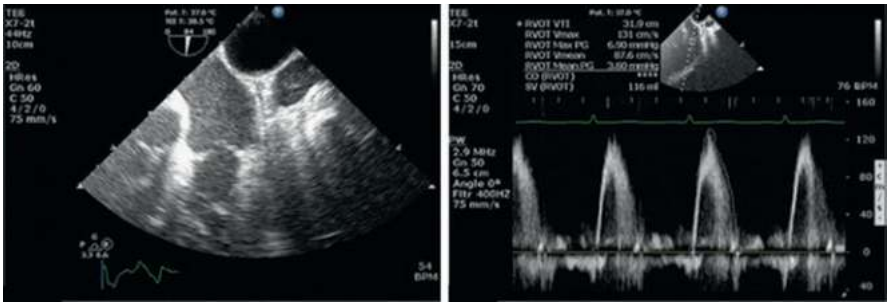

Fig. 6.6 TEE assessment of delta VTI % or delta Vpeak % can also be done using the upper esophageal aortic short axis view so that the pulsed wave Doppler signal is parallel to the right ventricle outflow tract

used successfully to assess fluid responsiveness by measuring variations in aortic blood flow (ABF) using the following formula:

$$\text{Delta ABF\%} = \left(\text{ABFmax} - \text{ABF min}\right) \ / \ \text{ABFmean} \times 100$$

where ABFmax and ABFmin are the maximal and minimal peak ABF values over 1 respiratory cycle, respectively and ABFmean equaling (ABFmax + ABFmin)/2. The delta ABF value is typically averaged over five respiratory cycles [22, 28, 29].

Passive Leg Raising Test for the Prediction of Volume Responsiveness in the Spontaneously Breathing Patient (Combined with Changes in Stroke Volume)

Mechanical ventilation-induced changes in hemodynamic signals cannot be used in predicting fluid responsiveness in spontaneously breathing patient. Passive leg raising (PLR), by lifting the legs passively from the horizontal position, induces a gravitational transfer of blood from the lower extremities toward the intrathoracic compartment [1]. In order to induce sufficient venous blood shift that can create a significant increase in cardiac preload, the lower limbs are elevated to 45° (automatic bed elevation) while simultaneously placing the patient in the supine from a 45° semirecumbent position. TTE measurement of stroke volume before (at baseline) and after passive leg raising can predict fluid responsiveness. An increase in stroke volume by 12% or more during passive leg raising is highly predictive of positive hemodynamic response and stroke volume increase with subsequent fluid bolus administration [30, 31].

On a parasternal 2D view, aortic diameter is measured just below the level of the aortic annulus at the left ventricle outflow tract (LVOT). Aortic valve area (AVA) is calculated as follows:

$$\mathrm{AVA} = \left(\pi\left[\mathrm{pi}\right] \times \mathrm{LVOT\ \ diameter}^2\right) / 4 = 0.785 \times \mathrm{LVOT\ \ diameter}^2$$

On an apical 5-chamber view, aortic blood flow is recorded using pulsed Doppler, with the sample volume placed just below the aortic annulus. The velocity–time integral of aortic blood flow (VTIa) is calculated. Stroke volume is then calculated as SV = VTIa × AVA and CO is calculated as SV X HR. The aortic valve area is only measured once at baseline since it is considered to remain unchanged. To reduce error in VTI measurement, 3–5 consecutive measurements averaged over one respiratory cycle are reported for each VTI measurement [30].

Echocardiographic measurements to detect changes in VTIa require experienced echocardiographers to perform the measurements, especially because the changes in VTIa may not persist beyond a couple of minutes. In addition, any malalignment of the pulsed Doppler beam can introduce errors in measurements mainly due to underestimation of the VTI caused by angulation of the Doppler beam if not strictly parallel to the aortic blood flow (a 15° angle inducing a 5% error in measurement) [32].

In mechanically ventilated patients, esophageal Doppler measurements of changes in descending aortic blood flow in response to passive leg raising have been used in several studies [29, 33, 34]. Since these probes are uncomfortable in conscious spontaneously breathing patients, they are not used in non-intubated patients.

Conclusion

Several echocardiographic methods for the assessment of volume status and the prediction of fluid responsiveness have been described. Echocardiographic "dynamic" measures for the assessment of fluid responsiveness in mechanically ventilated patients include SVC and IVC collapsibility index, left (and right) ventricle delta velocity time integral percentage, left (and right) ventricle delta peak velocity percentage, and delta aortic blood flow percentage.

In the spontaneously breathing patient, the only validated test for assessment of fluid responsiveness is the passive leg raising test and requires the simultaneous transthoracic echocardiographic assessment of changes in aortic velocity time integrals or peak velocities as a dynamic measure of fluid responsiveness.

A detailed understanding of the various limitations of these echocardiographic measurements is essential in avoiding the wrong decision-making regarding fluid loading.

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Microcirculatory Blood Flow as a New Tool for Perioperative Fluid Management

7

Daniel De Backer

Abstract

Microcirculatory alterations often occur in the perioperative setting under the influence of multiple factors including hypovolemia, impaired cardiac function, vasoplegia, anesthetic agents, surgical trauma, ischemia/reperfusion injury and sepsis. The severity and duration of these alterations has been related to the outcome of these patients. This systematic review will report to which extend these microvascular abnormalities can be affected by fluid administration.

Administration of fluids usually improves microvascular dysfunction by increasing the perfused capillary density. Importantly, there is an important variability among the patients. Timing of the intervention has a huge impact as early interventions often led to an improved microvascular perfusion while delayed intervention often fails to improve the microcirculation. Of note the impact of fluids on the microcirculation is relatively dissociated form its systemic effects and can thus not be predicted by changes in cardiac output or blood pressure. Changes in lactate or in veno-arterial PCO2 gradients can be useful to indirectly evaluate the microvascular effects of fluids. Even though colloids are often associated with greater effects than crystalloids in experimental settings, this has not been confirmed in patients. Finally the impact of red blood cell transfusions is highly variable and may depend on the severity of microvascular alterations at baseline.

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Introduction

Tissue perfusion is often altered in the perioperative setting, as a result of decreased organ perfusion associated to low cardiac output and/or hypotension. However, alterations in microvascular perfusion can also contribute to impaired tissue perfusion and this has only recently been recognized. The severity and duration of these alterations have been related to the development of perioperative organ dysfunction [1].

Fluids are administered in the perioperative setting hoping that the increase in cardiac preload would result in an increased organ perfusion and in tissue perfusion. As microvascular perfusion is relatively independent from systemic perfusion [2–4], the impact of fluids on the microcirculation is not straightforward. We performed a systemic review (Pubmed search April 2019 using the following keywords: fluids, crystalloids, colloids, albumin, starches, hypertonic lactate, transfusions, microcirculation, microvascular, capillary) to discuss how fluids can influence microvascular perfusion.

Characterization of the Microvascular Alterations Observed in the Perioperative Setting

Several types of microvascular alterations may occur in the perioperative setting (Table 7.1). These are due to several factors including bleeding, impaired cardiac function, infection, tissue trauma, ischemia/reperfusion injury which can influence microvascular perfusion in different ways. Of note, multiple factors can of course occur simultaneously and have, sometimes, opposing influences. Accordingly, the incidence, nature, and severity of the microvascular alterations in the perioperative setting will depend on the contribution of these different factors, in conjunction to some predisposing factors related to the host such as advanced age, chronic

Table 7.1 Type of microvascular alteration according to the type of mechanisms

Mechanism	Effector	Microvascular alteration
Bleeding	Low cardiac output leading to impaired organ perfusion	Homogeneous decreased perfusion in all vessels ± decreased vascular density
Cardiac dysfunction		
Vasoplegia	Decreased perfusion pressure leading to impaired organ perfusion	
Anesthetic agents	??	Decreased vascular density/stop flow in some capillaries while others remain well perfused/ heterogeneity between areas
Sepsis	Activation of inflammation and coagulation pathways	
Tissue trauma		
Ischemia/ reperfusion		

Several mechanisms can coincide

cardiovascular diseases, diabetes, cirrhosis,…These factors will also affect the microvascular response to fluids.

Hypovolemia (bleeding) and impaired cardiac function (either pre-existing or induced by anesthetic agents or sepsis) may result in an impaired cardiac output which directly alters perfusion to organs, and especially less vital organs such as muscle, kidney and splanchnic region. Similarly, hypotension, as a result of decreased vascular tone under the influence of anesthetic agents, sepsis or ischemia/reperfusion injury, is also associated with blood flow redistribution among the organs and also results in hypoperfusion of some organs. These alterations are mostly characterized by a homogeneous decrease in perfusion in all microvascular vessels including arterioles and capillaries. One can expect this type of alterations to be sensitive to fluids, provided the heart is preload responsive, or alternatively to inotropes and vasopressors.

Infection and sepsis are associated with activation of inflammation and coagulation that result in diffuse endothelial dysfunction. Sepsis-associated alterations in microvascular perfusion are characterized by a decrease in capillary density and decreased proportion of perfused capillaries leading to heterogeneous tissue perfusion [5–7]. In the perfused vessels flow is usually already quite high and often excessive regarding to oxygen requirements of the perfused area. These kinds of alterations generate pouches of hypoxia in close vicinity to excessively perfused area, associated with explaining the high lactate levels and high venous oxygen saturation. This process is not fixed, as capillary perfusion may change minute by minute, and non-perfused capillaries suddenly become perfused and vice-versa. The capacity of the microcirculation to react to stress conditions is completely blunted. In opposition to normal conditions in which the microcirculation decreases its minimal heterogeneity when submitted to hypovolemia, the heterogeneity further increases in the septic microcirculation, leading to a mismatch between flow and oxygen requirements [8].

Anesthesia, tissue trauma and ischemia/reperfusion injury are associated with similar types of activation of the inflammatory cascade. Accordingly, microvascular alterations similar as those described in sepsis are often encountered, even though usually less severe. Anesthetic agents induce some microcirculatory alterations, usually limited in intensity and rapidly resolving after cessation of the infusion of the anesthetic agent [9]. In patients submitted to cardiac and non-cardiac surgery, we demonstrated that microvascular alterations occur already at the onset of anesthesia, worsen during the surgical procedure and slowly recover afterwards [10]. The severity of these microvascular alterations was related to the type of surgery and was associated with degree of organ dysfunction the day after surgery. In patients with trauma, microvascular alterations were observed after hemodynamic stabilization and their severity was related with organ dysfunction [11]. It is important to realize that the combination of multiple kind of injuries (hypovolemia/inflammation/hypoxemia) can further exacerbate these microvascular alterations. In experimental conditions, the effects of hypovolemia combined with hypoxemia generated more alterations to the intestinal microcirculation that any of these in isolation [12].

To improve these heterogeneous alterations, interventions should be able to recruit the microcirculation rather than increasing flow in the already perfused vessels.

The Risks of Fluid Administration for Microvascular Perfusion

The administration of asanguinous fluids carry the risk induced of hemodilution. The impact of hemodilution on the microcirculation are quite variable. On one hand hemodilution decreases blood oxygen carrying capacity, and this may impair tissue oxygenation. On the other hand it also decreases viscosity which may have opposing effects on microvascular perfusion, depending on the hematocrit level. As resistance to flow is proportional to viscosity of the blood, a decrease in viscosity can be associated with an increased red blood cell velocity. However, maintenance of minimal level of viscosity is also needed to maintain microvessels open. At high hematocrit levels, the decrease in viscosity is associated by a decreased resistance to flow and hence improves perfusion especially at the capillary level [13]. At low hematocrit, the decrease in viscosity may favor vessels collapse and thus impair flow [14].

Due to the increased permeability, administration of fluids can also increase tissue edema. While edema can theoretically increase diffusion distance for oxygen, this effect is usually limited. More importantly, tissue edema may also increase interstitial pressure, especially in the splanchnic organs. Even a minimal increase in interstitial pressure can be associated with an impaired microvascular perfusion and adhesions of white blood cell to the endothelium.

Finally, there is also a risk that fluids administration may impair tissue perfusion by increasing venous pressure. Even though it was reported in one observational trial that a high central venous pressure after fluid resuscitation was associated with an impaired microvascular perfusion in patients with sepsis, it was difficult to separate the impact of the severity of disease from the impact of increased back pressure (as patients with more severe cardiovascular dysfunction also have higher CVP for the same blood volume) [15].

Impact of Fluids on Microvascular Perfusion: What is the Evidence?

Hypovolemia is associated with a decrease in microvascular perfusion. In patients submitted to hemodialysis, fluid withdrawal was associated with microcirculatory alterations that were more prominent in capillaries [16].

In experimental studies, fluid administration resulted in an improvement of microvascular perfusion [17, 18]. In patients submitted to high risk surgery, administration of fluids improved microvascular reactivity [19]. A recent trial demonstrated the simultaneous occurrence of indices of preload responsiveness and

microvascular alterations in patients submitted to major abdominal surgery [20]. Furthermore, correction of hypovolemia improved microvascular perfusion in these patients [20]. In patients with septic shock, fluids administration was usually associated with an improvement in the proportion of perfused capillaries resulting in an increased perfused vascular density [21–24], even though some individual variability in the response was observed. When microvascular perfusion increased, it also decreased heterogeneity between areas [21] further indicating that the diffusive component of the microcirculation markedly improved. It also resulted in a decrease in veno-arterial and ear lobe tissue PCO2 gradients [25], which are indirect markers of microvascular perfusion [26, 27].

As the response to fluids was somewhat variable, it is important to understand what could be the factors predicting a positive microvascular response. One of the factors may be the relative adequacy of the microcirculation at baseline, fluids being more effective when microcirculation is more altered at baseline than when closer to normal [23, 28]. Importantly, the microvascular response in these various studies was often dissociated for the systemic response [21, 22, 24]. The improvement in microvascular perfusion was observed in patients responding or not to fluid challenge by an increase in cardiac output or arterial pressure [21]. On the other hand, patients increasing their cardiac output or blood pressure in response to fluid did not always experienced an increase in microvascular perfusion. Of note, the magnitude of the increase in microvascular perfusion was correlated with the magnitude of the changes in lactate levels (Fig. 7.1), highlighting that microvascular perfusion is the key determinant of tissue perfusion [21]. At the bedside, changes in lactate and

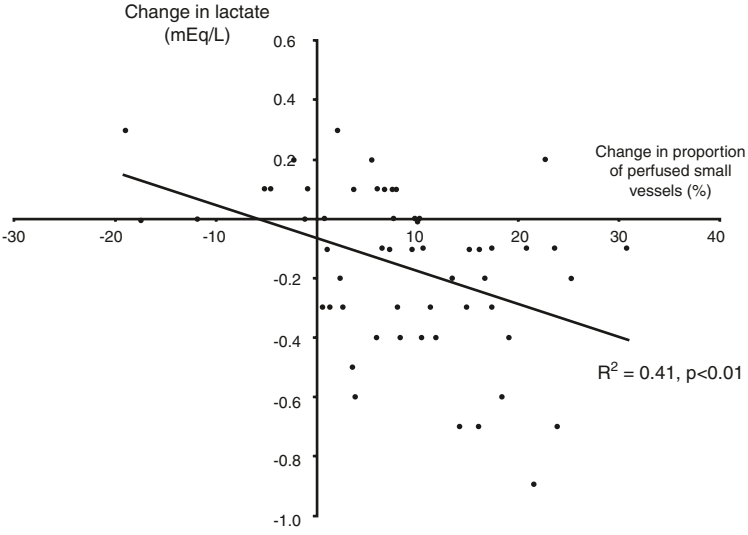

Fig. 7.1 Relationship between changes in microvascular perfusion and changes in lactate levels. Derived from Ospina et al. [21]

veno-arterial PCO2 gradients can thus be used to indirectly evaluate the microvascular response to fluids. Even more importantly, organ function improved the next day in patients experiencing improvements in microvascular perfusion in response to fluids but not in the others [23].

A positive response to fluids may be observed only at early stages of the disease. In experimental sepsis, fluid administration failed to improve the heterogeneity of blood flow distribution when given in a delayed fashion while these were effective at earlier stages [29]. In patients with septic shock, fluids improved microvascular perfusion when administered within 24 h of the onset of sepsis but not after 48 h [21].

Finally, a large amount of fluid is probably not needed. In patients with septic shock, Pottecher et al. [20] showed that the first bolus of fluid improved microvascular perfusion while the second bolus failed, even though it further increased cardiac index. This seems to indicate that the impact of fluid may be saturable.

Colloids Versus Crytalloids

There is an ongoing debate on whether colloids have a greater effect on the microcirculation compared to crystalloids. Theoretically, one may expect that crystalloids may better preserve microvascular perfusion and limit capillary leak, potentially by better preserving the glycocalyx [30–33].

In experimental studies, colloids often increase more significantly microvascular perfusion compared to crystalloids both in ischemia reperfusion injury [33] and in sepsis [17]. In addition, colloids also had a favorable impact on adhesion of white blood cells and platelets to the endothelium [17, 33]. In humans, very few studies compared the impact of colloids to crystalloids on the microcirculation. In 60 patients with septic shock, albumin and Ringer's Lactate similarly improved the sublingual microcirculation [21]. These results contrast with the findings of Dubin et al. [34] who reported that hydroxyethystarch better preserved the sublingual microcirculation of patients with septic shock compared to saline. Of note, the microcirculation was not evaluated at baseline making difficult to differentiate a positive impact of the type of fluid from an imbalance at baseline in this very small series of patients. Another factor may be related to the comparator as the effects of balanced crystalloids may differ from those of saline. In experimental sepsis, balanced solutions ware associated with better preserved microcirculation compared to saline [35]. Half molar lactate may even better protect the endothelium than saline of similar osmolarity, resulting in a better preserved microcirculation [36]. Accordingly, experimental studies almost unanimously point out some beneficial effects of colloids, and especially albumin, over crystalloids on microvascular perfusion, but it is difficult to ascertain that these differences can also be observed in critically ill patients.

Red Blood Cell Transfusions?

Red blood cell transfusions should always be considered as an alternative to asanguinous fluids in order to increase oxygen delivery to the tissues. The main difficulty in predicting the potential impact of red blood cell transfusions is that microvascular hematocrit is lower but not directly proportional to systemic hematocrit. The mandatory plasma layer of a few microns at the surface of endothelial surface represents a greater proportion of vessel volume in small than in large vessels, reported as Farheus effect (Fig. 7.2). In addition, the distribution of hematocrit varies at bifurcations due to kinetic inertia of red blood cells: hematocrit is larger in vessels with a small angles according to originating vessel than in vessels with a larger angle [37] (Fig. 7.3).

While experimental studies often demonstrated an improvement in microvascular perfusion and tissue oxygenation with red blood cell transfusions [38, 39], their effects are more variable in perioperative or septic patients [40–44]. In patients submitted to cardiac surgery, transfusions increased capillary density but not microvascular flow [44]. In another series of postoperative patients the effects of transfusions were more mitigated [43]. In patients with sepsis, there were no effect in most trials [40, 42, 45] while some others found beneficial effects [41]. In patients with trauma, transfusions also were associated with variable effects [46].

Obviously, there is a huge individual variability in the response to red blood cell transfusions, as demonstrated in the trials that reported individual responses, with markedly positive effect in some patients, absence of effects in others, and a markedly negative effect in the remaining patients. The magnitude of the effect is far above the intrinsic variability of the measurements. The direction of the effect may

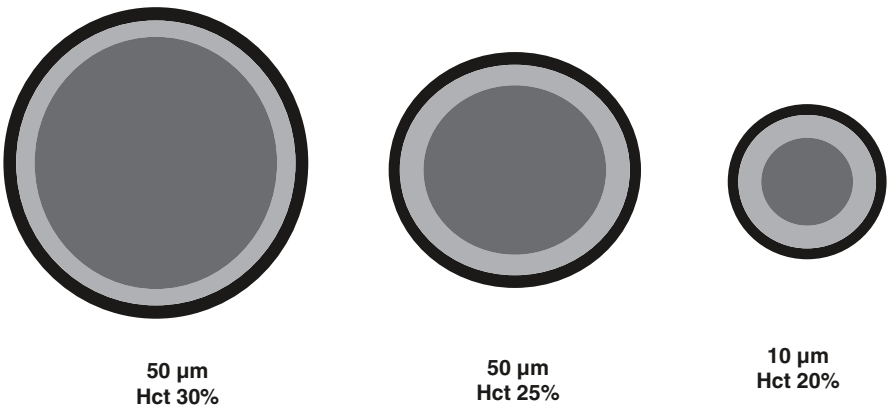

Fig. 7.2 Microvascular hematocrit differs according to the size of the vessel. Due to a mandatory plasma layer of a few microns at the surface of the endothelium, the microvascular hematocrit decreases with vessel size

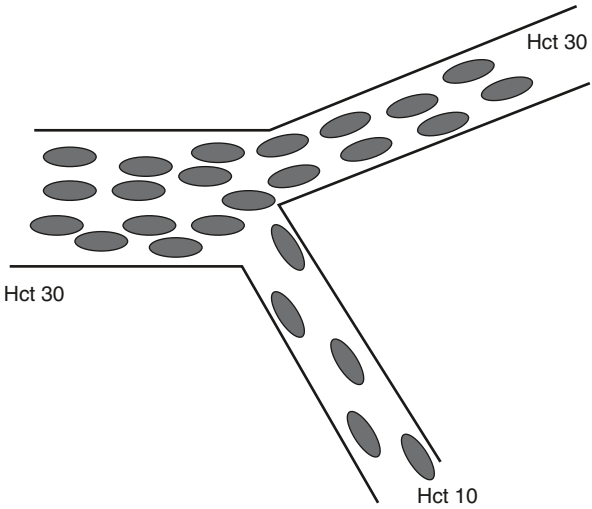

Fig. 7.3 Variability of hematocrit in branch vessels. Due to kinetic inertia of red blood cells, hematocrit is higher in vessels with minimal angle with source vessels compared to vessels with larger angle

depend on the severity of the underlying microcirculatory alterations at baseline, with an improvement in microcirculatory perfusion and tissue oxygenation in patients with alterations in these variables at baseline but also deterioration of these in the patients who had less altered microcirculation variables at baseline [40, 42, 46]. The effects of transfusions on the microcirculation were not related to baseline hemoglobin levels nor with the changes in systemic hemoglobin levels [40, 42].

Based on preclinical observations [38], it has been suggested that transfusions of young red blood cells but not old red blood cell could improve the microcirculation. In a limited size single centre randomized trial in postoperative patients, transfusion of young red blood cells was associated with a greater improvement in microvascular perfusion than when red blood cells older than 3 weeks were transfused [43]. In other trials, the age of red blood cells was not affecting the response to transfusions in critically ill patients [45], after cardiac surgery [47] and in septic patients [40]. Hence, the impact of age of red blood cells on microvascular response remains questionable. Of note this is in accordance with a large randomized clinical trial that failed to demonstrate an impact of the age of red blood cells on outcome, including on organ dysfunction [48].

How Can We Assess the Microcirculation at Bedside?

Videomicroscopic techniques use the reflection by deeper tissue layers to illuminate the tissue to investigate, and several methods to discard the light reflected by superficial layers. Orthogonal polarization spectral (OPS), Sidestream Dark-Field (SDF), and Incident Dark-Field (IDF) are three imaging techniques that can easily be applied at the bedside in critically ill patients. These techniques are mostly used to study the sublingual area [21, 49], which is supposed to reflect other organs when

diffuse alterations are observed, such as in sepsis [5], but may fail to track microcirculatory alterations that may occur to organs submitted to increased interstitial pressure (such as in abdominal compartment syndrome). The use of this technique requires some training and, more importantly, may be difficult to obtain in agitated patients or in patients under noninvasive mechanical ventilation. Evaluation of the microcirculation is often done by semi-quantitative scores [50] which are highly reproducible and often more reliable than currently available semi-automated analysis software [51]. This semi-quantitative analysis can even be reliably performed at bedside by trained nurses [52].

The microcirculation can also be indirectly evaluated. Tissue PCO2 and venoarterial PCO2 gradients are particularly attractive. Tissue PCO2 reflects the balance between CO2 production (and thus metabolism) and perfusion, and therefore can be used to indirectly evaluate tissue perfusion [27]**.** Tissue PCO2 can be measured by contact probes at ear lobe or on the stomach (but gastric tonometry is no more available). Tissue PCO2 measurements can detect zones of impaired perfusion and/or tissue hypoxia even when perfusion is heterogeneous, as the measured value reflects the most abnormal value in the sampled volume. *Venoarterial gradients in PCO2 (PvaCO2) can also be used to evaluate microvascular perfusion. In a series of 75 patients with septic shock in whom sublingual microcirculation and PvaCO2 were measured, a PvaCO2 value greater than 6 mmHg was associated with moderate alterations in sublingual microcirculation and values above 10 mmHg were associated with very severe microvascular alterations. More importantly, changes PvaCO2 were inversely related with changes in microvascular perfusion* [27]. *HencePvaCO2 measurements can thus be used to indirectly assess the microcirculation, especially when venous oxygen saturation is normal.*

Conclusions

Microvascular perfusion is often altered in patients in the perioperative period, especially in high risk surgical patients and in the context of sepsis. Hypovolemia, anesthesia and surgical trauma, in addition to a potential underlying infection, may contribute to microvascular alterations, and hence in alterations in tissue perfusion and oxygenation.

Fluids often improve microvascular perfusion if given early in the course of the disease and this effect is somewhat dissociated form the systemic effects of fluids. The advantage of colloids over crystalloids suggested in experimental studies has not been demonstrated in critically ill patients. The effects of red blood cell transfusions are highly variable and seem to be dependent on the alterations in microcirculation at baseline.

Key Points

- Microvascular alterations frequently occur in the perioperative setting
- Fluids improve functional capillary density but this effect can be variable

- The microvascular effects of fluids cannot be predicted from their systemic effects
- An improvement in microvascular perfusion after fluid administrations is associated with an improvement in organ function
- The impact of red blood cell transfusions is highly variable

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Mean Systemic Filling Pressure Is an Old Concept but a New Tool for Fluid Management

8

Hollmann D. Aya and Maurizio Cecconi

Abstract

Purpose of the review: Most of our blood volume is contained in the venous compartment. The so-called "compliant veins" are an adjustable blood reservoir that is playing a paramount role in maintaining hemodynamic stability. Several autonomous reflexes govern the capacity of this reservoir. The mean systemic filling pressure (Pmsf) is the pressure in the cardiovascular system when there is no blood flow, and is pressure that can describe the capacitance of the venous reservoir. This pressure can be measured in human patients by both non-invasive or minimally invasive methods. However, the significance of this hemodynamic variable is still not fully understood. The purpose of this review is to summarize what is known about the venous reservoir and the Pmsf and how we can use this information to assess the cardiovascular state of critically ill patients.

Findings: The venous tone is governed by sympathetic reflex, mainly related to barocerectors via α(alpha)-adrenergic stimulation and to chemoreceptors. The vasoconstriction affects significantly the capacitance of the system by shifting blood between the stress and non-stress volume compartments. The Pmsf is the pivot pressure of the circulation, and a quantitative index of intravascular volume, and it is also governed by the mechanisms that affect the venous tone. Pmsf can be measured at bedside by three methods described in critically ill patients. This pressure can be also modified by fluid therapy and vasoactive medications.

Pmsf along with other haemodynamic variables can provide valuable information to correctly understand the cardiovascular status of critically ill patients

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and better managing fluid therapy and cardiovascular support. Future studies using Pmsf will show its usefulness for fluid administration.

Key Points

1. The venous system serves a blood reservoir adjustable to the blood flow requirements.
2. The venous tone is governed by the sympathetic activity via baroreceptors (using α[alpha]-adrenergic receptors) and chemoreceptors.
3. The Pmsf is a quantitative measurement of the volume status and represents a measurement of the venous reservoir tone.
4. Pmsf can be measured at bedside by using inspiratory hold maneuvers, by using a stop-flow arterial-venous equilibrium pressure or can be estimated using a computerized mathematic algorithm.
5. Pmsf monitoring can provide important information when a clinician wants to challenge the system using a bolus of fluids or a passive leg raising (PLR) test. It can also guide decisions regarding the use of further fluid or vasoconstrictors.

Introduction

The assessment of the intravascular volume status in critically ill patients is crucially important and enormously challenging. The importance is based on the evidence that both hypovolemia and fluid overload are dangerous situations in critical illness [1–4]. The challenge consists in finding a parameter able to provide information about the intravascular filling independently from other confounders such as cardiac function, vascular tone or preload reserve. Cardiac preload is defined as the end-diastolic myocardial stretch (sarcomere tension), which in clinical practice is impossible to measure. Hence, some indicators of preload have been suggested: right atrial pressure (RAP) and its surrogate central venous pressure (CVP) are considered static measurements of right ventricular preload. The problem with this pragmatic approach is that clinical values of CVP do not accurately reflect preload. For example, when cardiac function decreases, CVP increases immediately without changes in intravascular volume. The mean circulatory filling pressure can quantify the intravascular filling independently from the cardiac function: it is the mean pressure that would be measured at all points in the cardiovascular system if the heart were stopped suddenly and the blood were redistributed rapidly between the arterial and venous territory [5]. This pressure is equal to the pressure at the pivotal point of the circulation, which is assumed to be located in the capacitance vessels. This pressure depends on the stressed volume and the capacitance of the system (Fig. 8.1). Therefore, in order to better understand hemodynamics at the bedside, it is essential to know the factors that affect the capacitance vessels, which are basically the venous system. In this chapter, we review some basic concepts of venous physiology that provide useful tools to manage patients in intensive care.

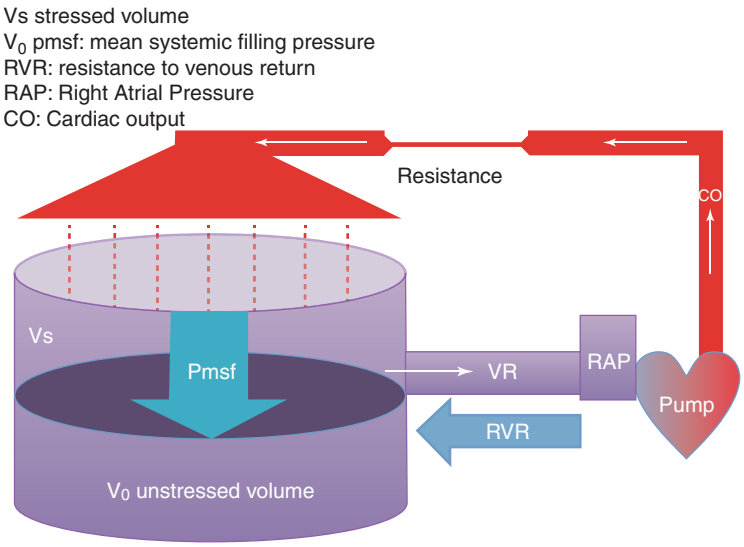

Fig. 8.1 Model of the systemic circulation. Circulatory model with two reservoirs: the big venous reservoir, mainly located in the splanchnic venous territory and the small reservoir, just before the pump: the right atrium. The bigger size of the venous segments suggest a bigger volume and also a greater distensibility, compared with the lower compliances of the arterial segments. The segments between compartments represent the resistances, which are more variable at the arterial segments. The separation between the stressed and unstressed volume represents the adjustable capacitance of the venous reservoir

The Venous System

The venous system is not merely a conduct of blood to the heart. It works as an adjustable blood reservoir, able to modify blood flow according to changing metabolic demands. Veins contain 70% of total blood volume, whereas arteries contain only 13–18%, and capillaries 7% [6, 7]. Venous walls have a much larger compliance compared to arterial walls. Let us imagine this "blood reservoir" as a distensible compartment. The volume required to fill a distensible tube, such as a tire or a blood vessel, with no pressure rise is called the "unstressed" volume (V_o). At this point, the volume depends on the total capacity (or capacitance) of the reservoir, since the pressure is zero. Further volume expansion will imply necessarily a pressure rise and an elastic distension of the tube wall. He relationship between pressure and volume defines the compliance (C) of the reservoir walls. This volume is the "stressed" volume (V_s) and is related to the pressure (P) in the equation:

$$P = V_s / C$$

As with other parts of the vascular system, the vein's walls are composed of three basic histological layers: the tunica intima, the tunica media, and the tunica adventitia. The tunica media contains a variable thick layer of vascular smooth

muscle cells. These cells can be stimulated to contract by multiple mechanisms: nervous reflex signals, hormonal stimulation, by stretching the smooth muscle, and several other ways. We are going to examine some of these mechanisms.

Arterial Baroreceptor Reflex Influence

Arterial hypotension reduces baroreceptor activity and provokes an increased sympathetic discharge, which causes venoconstriction, arterial vasoconstriction, and increased cardiac contractility and heart rate. The classic studies from Heymans and colleagues [8] demonstrated the influence of the carotid sinus baroreceptors on the blood volume of the mesentery, spleen, liver, and intestine. Most of the change observed in vascular capacitance takes place in the splanchnic bed.

Shoukas et al. [9] studied the reflex control of the total systemic vascular capacity in vagotomized dogs, measuring blood volume shifts caused by the carotid sinus reflex by diverting venous return into a reservoir while cardiac output and central venous pressure were maintained at a constant level. The isolated carotid sinus pressure (ISP) was lowered or raised in 25 mm Hg steps between 75 to 200 mm Hg. This procedure mobilized blood into (when decreasing ISP) or out (when increasing ISP) of the reservoir indicating a decrease or an increase in total vascular capacity, respectively. They observed that the total volume shift was approximately 7.5 mL/Kg for ISP changes from 75 to 200 mm Hg, whereas when the arterial blood pressure was controlled at 75 mm Hg, the total volume shift was 260 ml for the same change in ISP. This greater change in reservoir volume with fixed mean arterial pressure demonstrated the total influence of the carotid reflex system on the total capacity of the systemic vascular bed. The volume change with uncontrolled mean arterial pressure indicates the actual blood volume that the overall reflex system mobilizes as it changes vascular resistance and capacity. As the reflex did not affect the total systemic and arterial compliances, the authors concluded that the reflex controls the total systemic venous capacity to a degree that changes cardiac output potentially by 30–40% per 25-mm Hg change in ISP. Similar results were reported by Hainsworth [10] in an experiment where the aortic arch was stimulated and a hind limb of a dog was vascularly isolated with blood pumped at constant flow. They observed that the large superficial veins of the dog's hind limb participate in the baroreceptor reflex. Likewise, Shigemi et al. [11] showed in an elegant study that α(alpha)-adrenergic mechanisms contribute significantly to active changes in systemic venous capacity, whereas the β(beta)-adrenergic system has very little effect on the active changes in venous vessels, but does contribute to the overall capacity by reducing the venous (hepatic) outflow resistance when the carotid sinus baroreflex system is activated. The *active* changes are those due to changes in vascular compliance (the slope of the pressure-volume relationship) or changes in unstressed vascular volume or vascular capacity in contrast with *passive* (physical) changes in the vascular capacity, defined as movements along the same pressure-volume curve secondary to a change in the blood flow and concomitant changes in vascular distending

pressures. In this study, 14 dogs were vagotomized and anesthetized, and the carotid sinus were isolated. A constant flow, constant central venous pressure cardiopulmonary bypass was used to determine changes in vascular capacity. The changes in unstressed vascular volume were calculated when carotid sinus pressure was reduce from 200 to 50 mm Hg first without any adrenergic receptor antagonist, then with either an α(alpha)-(phentolamine) or a β(beta)-(propranolol) antagonist, and then with both. The change in unstressed volume in the systemic circulation was reduced by 72% with phentolamine, by 35% with propranolol, and by 73% with both antagonists. This suggests that the α(alpha)-adrenergic mechanism predominates over β(beta)-adrenergic mechanism in the active control of venous capacity by the carotid sinus baroreflex system [12]. The β(beta)-adrenergic mechanism may play a role in passive capacity changes. Both active and passive changes in vascular capacity contribute to the regulation of cardiac filling and therefore cardiac output. The β(beta)-adrenergic stimulation effect on the venous system is controversial; some authors reported a venodilation effect [13, 14] while others concluded that β(beta)-receptor stimulation induces blood redistribution from the periphery to the heart by reducing general venous resistance [15, 16] or hepatic outflow resistance [11, 17].

During hypovolemia these reflexes cause venoconstriction, sending blood back to the central circulation. Actually, even after 20% of the total blood volume has been lost, the circulatory system functions almost normally because of this variable reservoir function of veins [6]. Similarly, when a person is standing absolutely still, the pressure in the veins of the feet is about 90 mm Hg simply because of the gravitational effect of the blood in veins. This effect could actually be life threatening if there was no compensatory reflex. Hainsworth [18] pointed out that almost all the possible venoconstriction reflex is used to maintain cardiac output (CO). Venous tone is thus very important in hemodynamic hemostasis.

Chemoreceptor Reflex Influence

Studies by Kahler and colleagues [19] showed in a preparation where dogs were pump perfused from a blood reservoir and oxygenator to which venous blood returned, during hypoxia (SaO2 50%) the volume of the reservoir increased by 16 ± 2.8 mL/Kg. After splenectomy and bilateral adrenalectomy, the change was only 10.9 mL/Kg. They concluded that hypoxia generates venoconstriction, but circulating catecholamines are also necessary for the full response. Breathing 5% of carbon dioxide in air causes an increase in CO in people, while changes in arterial pressure and heart rate are relatively small [20]. The change in CO can be also related to the hyperventilation, but Price et al. concluded that an increase in sympathetic activity was the primary reason.

Smith and Crowell [21] tested the response of the mean circulatory filling pressure (MCFP) and CO to hypoxia by ventilating dogs with 8% oxygen in nitrogen. MCFP increased 27% while RAP decreased; there was a 15% increase in arterial pressure and 45% increase in CO, suggesting a significant venoconstriction with

increased cardiac contractility. With reflexes blocked with spinal anesthesia, the MCFP resistance for venous return and arterial pressure fell during hypoxia while CO and RAP did not change.

Moderate hypercapnea and hypoxia have little direct non-reflex effect on CO and Pmsf [22]. Severe hypercapnea (PaCO2 to114 mm Hg [15.2 KPa]) caused an increase in Pmsf by 5.5 mm Hg, whereas a PaO2 of 34 mmHg (4.5 KPa) caused an increase in Pmsf by 2.5 mmHg [23].

The venoconstrictive effect of the veins of the limbs in mammals in response to chemoreceptor stimulation is not completely established, except under extreme conditions. Mild chemoreceptor stimulation has little effect on the capacitance system: It has little constrictive effect or even a dilating influence on skin and skeletal muscle veins of dogs [24–27]. The saphenous vein does not respond to either carotid or aortic chemoreceptor stimulation [26–29].

The Capacitance Vessels

Veins cannot be considered a pharmacologically homogeneous system [30, 31] and their overall response to stimulus is very difficult to predict. Certain parts of the venous system are particularly compliant: these include the spleen, the liver, the large abdominal veins and the venous plexus beneath the skin. Splanchnic and cutaneous veins have a high population of α(alpha)1- and α(alpha)2-adrenergic receptors, so they are very sensitive to adrenergic stimulation, contrary to skeletal and muscle veins [32]. There are nerve terminations in the proximity of many small vein smooth muscles [33] but not in the veins of skeletal muscle [34]. However, circulating catecholamines can induce contraction of venules and veins of skeletal muscle and mesentery [33, 34]. Thus, probably catecholamines released from the sympathetic nerve termination of the arterial side may pass through the capillary bed and affect the venous system.

Some authors consider it reasonable to assume that all parts of the capacitance system would act as a unit in cardiovascular homeostasis [7, 35] although lack of response of one part of the system (i.e., limb veins of people) should not be considered as evidence that others parts of the system (i.e., the splanchnic bed) are also nonreactive to stimulation. Cutaneous veins respond vigorously to temperature regulation reflexes [35, 36] whereas the splanchnic veins are more involved in the reflex system for cardiovascular homeostasis. Moreover, the effect of changes in sympathetic activity with baroreceptor stimulation is not uniform on the venous tone in different organs such as the spleen, kidney, or heart [37, 38] and likewise the pharmacological response of veins from different organs [39].

Smooth muscle of the veins and arteries do not respond necessarily in the same way to chemical signals. Dihydroergotamine can activate the veins but not the arteries [40]. The venous system primarily has α(alpha)-adrenergic receptors [41–44]. Stimulation of the β(beta)-adrenergic receptors of arterioles cause vasodilation but has little effect on the veins [45, 46]. Angiotensin can increase Pmsf [45, 47]. Isoprotenerol, a β(beta)-adrenergic agonist, causes a decrease in Pmsf when veins

are constricted with angiotensin. On the other hand, vasopressin has very little effect on Pmsf [48] or on vascular capacity once reflex blockade [49] and similar results were reported regarding natriuretic peptides [50]. Nitroglycerin and nitroprusside decrease Pmsf and increase unstressed blood volume but do not change vascular compliance in ganglion-blockade dogs [51]. Verapamil and nifedipine increase venous return by reducing the resistance to venous return without changing the Pmsf, whereas nitroglycerin in small doses can reduce Pmsf without changes in resistance to venous return [52]. Diltiazem reduces both resistance and Pmsf increasing CO [52].

The splanchnic veins seem to be the major site of capacitance activity. Price et al. [53] observed that the splanchnic blood volume decreased by 500 mL after 1 l of hemorrhage in healthy male volunteers, while mean arterial pressure, heart rate, CO, and splanchnic vascular resistance did not change significantly from baseline. The authors point out active venoconstriction without simultaneous arteriolar vasoconstriction as an explanation of the results. Hainsworht et al. [54] studied the response of splanchnic vascular capacitance to changes in carotid sinus pressure in anesthetised dogs, perfused at constant blood flow and at constant pressure from the inferior vena cava. Vascular resistance responses were expressed as the changes in perfusion pressure and capacitance responses were determined by integrating changes in vena cava outflow. Decreasing the pressure in the isolated carotid sinuses over the whole baroreceptor sensitivity range increased mean perfusion pressure from 91 to 149 mm Hg (a 67% increase in resistance) and decreased mean capacitance by 111 ml. (5 ml kg^{-1}). However, the range of carotid sinus pressures over which capacitance responses occurred was at a significantly higher level than the corresponding range for resistance responses. Comparison of the reflex responses with the responses to direct stimulation of efferent sympathetic nerves shows that quantitatively similar responses of resistance and capacitance to those induced by a large step decrease in carotid pressure could be produced by stimulating maximally the efferent sympathetic nerves at 5 Hz. These results suggest that at all levels of carotid sinus pressure there is no difference in the impulse traffic to resistance and capacitance vessels. The difference in the ranges of carotid pressure for resistance and capacitance responses is due to the greater sensitivity of the capacitance vessels to sympathetic nerve activity.

The Mean Systemic Filling Pressure

When the heart pumps blood continuously into the aorta, the mean pressure in the aorta remains high, averaging 80–100 mm Hg. As the blood flows into the systemic circulation, the mean pressure falls progressively as low as the level of the right atrial pressure (RAP). When the heart stops, the arterial pressure falls down and the RAP progressively increases. At a certain point, blood will not be flowing, and the pressure will be the same in all parts of the circulatory system. This was called the *mean circulatory filling pressure (MCFP)*. When the pulmonary circulation is excluded, we call this the mean systemic filling pressure (Pmsf). This pressure was

described by Bayliss and Starling [55], and they figured out that somewhere in the circulation there must be a point where the pressure is not changing when the heart stops. Actually, during a cardiac arrest, the pressure in the small veins (<1 mm) and venules do not change substantially, they are the "pivoting point" of the system [56]. This pressure is less than the capillary pressure, close to the portal venous pressure and greater than the RAP. Its anatomic location is not necessarily at the same venous branching level in different organs. The importance of this pressure, rather than its anatomical location, is that it provides a quantitative measurement of the intravascular filling status independent from cardiac function: its value is equal to the Pmsf.

Later in 1952, Guyton [5] studied the central venous resistance by observing what was called the "static blood pressure." This pressure was measured in a preparation of anesthetized dogs after fibrillating the heart and once the arterial and venous pressure achieved equilibrium (30–50 s). In some cases he used a roller propulsion pump to bring blood from the arteries to the veins and to achieve the equilibrium in less than 20 s. A special external venous circuit was used in 37 experiments on open-chest dogs for the study of progressive resistance to the return of blood to the heart. They measured blood flow, arterial pressure, peripheral venous pressure, and RAP. As the blood flow decreased progressively to zero, the arterial pressure fell and the peripheral venous pressure rose slightly to approach arterial pressure. The extrapolated point of approach of these two pressures correlated with static blood pressures measured by heart fibrillation. Guyton described several values for the static blood pressure, and consequently the upper limit of venous pressure, under several conditions:

- 5.96 mm Hg within a few seconds after the hearts of normal dogs were fibrillated and before vasomotor reflexes could develop
- 17.0 mm Hg after developing the most powerful vasomotor constriction that could be attained by a Cushing reflex
- Unlimited values after giving infusions of fluid immediately before fibrillation of the heart, depending on the amount of fluid and how long before fibrillation it was administered

Later, Guyton [57] introduce the term mean *circulatory* filling pressure (MCFP) to refer to this static pressure. This term was chosen to make a distinction between the *systemic* circulation (excluding the pulmonary circulation) and the entire circulatory system, but it is actually the same concept described previously by Starling. Guyton realized that the MCFP is clearly affected by the vasomotor reflexes: The MCFP measured within the first few seconds after the heart stops beating is only about one-half the same pressure measured 30 s or more after the heart stops beating. In normal dogs, the MCFP was about 6.3 mm Hg, while in a dog under total spinal anesthesia the MCFP fell to 5 mm Hg. Increasing the vasomotor tone by giving a continuous infusion of epinephrine from minimal to maximal doses caused a maximal increase in MCFP up to 16 mm Hg. At very high rates of epinephrine infusion the MCFP was still raising slightly while the MAP was not increasing anymore.

Guyton [57] also observed that when massive volumes of fluids are given to a dog, the MCFP rises immediately and then falls along a negative exponential curve to approach almost the baseline value. Changes in hematocrit were also measured and he initially thought that as long as the fluid volume is excessive after the infusion, active leakage of fluid from the circulation occurs but this leakage ceases as soon as the MCFP approaches the baseline values. This was further studied later by Prather et al. [58] in an experiment: blood volume was expanded rapidly in 36 dogs using 500 ml of whole blood, 6% dextran-saline solution, or Tyrode's solution. The Tyrode's group returned to normal blood volume within 80 min whereas the blood and dextran groups showed 25% and 70% retention, respectively, 2 h later; both MCFP and CO increased from 2 to 3 times immediately after infusion in all groups and returned to baseline levels within 90–120 min. Indeed, these factors returned to normal even in the dextran and blood groups although the blood volumes were still elevated; since the MCFP returned to normal in 2 h despite continued elevation of blood volume it was concluded that considerable stress-relaxation of the circulation occurred. The increase in intrinsic vascular volume due to stress-relaxation was estimated to be 13% in the blood group and 32% in the dextran group.

Guyton [59, 60] also observed that it is actually the difference in pressure between two points, not any single pressure at any point of the cardiovascular system that determines the rate of flow. Given that most of blood is in the venous territory, the pressure at this point is particularly interesting. Guyton suggested that venous return must be defined by three parameters: MCFP, the right atrial pressure (RAP), and the resistance to venous return (RVR). This can be also mathematically represented as follows:

$$\mathrm{VR} = \left(\mathrm{MCFP} - \mathrm{RAP}\right) / \mathrm{RVR}$$

Guyton [61] proposed this concept after drawing venous return curves in recently dead dogs. He replaced the heart with a pump and controlled the right atrial pressure (RAP) by changing the minute capacity of the pump (adjusting the height of a Starling resistor). He also controlled the MCFP by increasing or decreasing the total quantity of blood. From these curves one can spot that for any given RAP, the greater the MCFP, the greater the venous return is. And importantly, under isovolumetric conditions, the greater is the RAP, the lower is the venous return. As during steady conditions, cardiac output (CO) and venous return are equal, MCFP plays an important role on the regulation of CO.

Guyton concluded that MCFP is the *driving* pressure for the venous return and the RAP is the *backpressure* against the MCFP, but this concept has not been exempted from controversy. Brengelmann [62–64] pointed out that in Guyton experiments flow was controlled to obtain a desired level of RAP; in other words, the independent variable was blood flow instead of RAP. From his point of view, what venous return curves really show is the steady-state relationship between the blood flow through the systemic vasculature and the RAP. The equation of the venous return proposed by Guyton follow the Poiseuille's equation structure that relates a pressure gradient with the magnitude of flow through a fixed conduct segment. Logically, pressure gradient and flow are a consequence of pumping, and that

is why Brengelmann concludes that the driving force of venous return is the same as the one for cardiac output: the pump. Brengelmann made a fair point by criticizing the role of the Pmsf or RAP as independent variables, which has been also pointed out by other authors [56]. In a closed loop system such as the cardiovascular system, no pressure is really independent of flow, except the PMSF. However, from a physiological perspective it does not make any sense that the heart (the pump) governs the level of blood flow. Quite the opposite, the normal heart finely matches the metabolic demand with the oxygen delivery. That is why in this maybe oversimplified model, the Pmsf, which is complexly regulated by the sympathetic system, governs blood flow.

Measurement of the PMSF in Humans with Intact Circulation

The challenge of measuring the venous tone is that Pmsf is not easy to measure in patients with an intact circulation. Schipke et al. [65] performed a fibrillation-defibrillation sequence in 82 patients to measure the Pmsf over 13 s. A true equilibrium pressure was not achieved, and the arterial-central venous pressure difference was 13.2 ± 6.2 mm Hg.

Pinsky [66] proposed a model in animals with an intact circulation to construct venous return curves observing the relationship between instantaneous changes in right ventricular CO and RAP during intermittent positive pressure recruitment maneuvers and then extrapolating the RAP value to zero CO. Pmsf calculated were similar to Pmsf measured during circulatory arrest. Other studies [67–69] have confirmed this linear relationship between VR and CVP and derived Pmsf from the regression equation in animal models with intact circulation. Maas and colleagues [70] applied the same rationale to study the effect of a 12-s inspiratory hold maneuver to three different steady-state levels on central venous pressure (CVP) and blood flow (CO) measured via the pulse contour method during the last 3 s in mechanically ventilated postoperative cardiac patients. This interesting study showed again a linear relationship between CVP and CO, and, importantly, Pmsf could be estimated in intensive care patients with an intact circulation. Obviously this technique is only feasible in fully sedated patients under mechanical ventilation. This method was also used by Keller and colleagues [71] to assess the changes of passive leg raising (PLR) on venous return: They observed nine postoperative cardiac patients at baseline, during PLR and after volume expansion (500 ml of hydroxyethyl starch). They reported a Pmsf at baseline of 19.7 mm Hg. This only increased to 22 mm Hg after PLR and to 26.9 mm Hg after volume expansion (VE). Although CO increased after PLR and VE, the gradient of pressure of venous return (difference between Pmsf and CVP) increased by 2 mm Hg after PLR and by 5.8 mm Hg after VE. This could explain why a PLR test does not systematically increase CO in fluid responsive patients [72], or even for a fluid challenge, the increase in Pmsf is an essential condition to effectively test the cardiac response.

The main problem of this method is the potential interaction of the hold-inspiratory maneuver with the values of Pmsf. An increase in the intrathoracic

pressure increases the RAP and the pressure backward in the venous territory. In a recent study, Berger et al. found that the inspiratory hold maneuver overestimate Pmsf by a mean difference of 3 mmHg [73]. On the other hand, it reduces cardiac output and arterial pressures, which can trigger baroreceptor reflexes from the aortic and carotid territories and generate venoconstriction.

Parkin and Wright [74] described a method for estimating a mean systemic filling pressure analogue (Pmsa) using the mean arterial pressure (MAP), RAP, CO, and anthropometric data. The calculation of Pmsa was fully described in other publications [75]. In essence, they used a mathematical algorithm to build a cardiovascular model using the patient's data. The clinical validity of this approach was tested in ten patients in acute renal failure receiving continuous vein-venous hemofiltration [76]. Fluid replacement therapy was electro-mechanically controlled to a target value of Pmsa. Despite some limitations of this study, this approach supports the concept of using Pmsa as a quantitative parameter of the intravascular volume status. This method was used to analyze hemodynamic changes after a fluid challenge (250 ml of colloids or crystalloids in 5 min) in patients admitted to intensive care [77]: Pmsa increased similarly in responders and non-responders, as expected but interestingly CVP increased more in non-responders, neutralizing the changes in the gradient of pressure of venous return as described by Guyton.

Recently, Gupta et al. [78] used Pmsa to investigate the performance of cardiac power (defined as the product of arterial pressure and cardiac output) relative to Pmsa (CP_{vol}). CP_{vol} represents a measurement of cardiac performance adjusted to the vascular tone. According to the authors, values below 0.047 of CP_{vol} have a high sensitivity (97%) and not so high specificity (57.5%) to predict fluid responsiveness.

Anderson [79] proposed a noninvasive technique to measure Pmsf by a rapid occlusion of the circulation in the arm (Pmsf-arm). Once the arterial (Pa) and venous pressures (Pv) in the arm equilibrate, the pressure measured would be Pmsf. The precision of this technique has been recently studied [80]. Four repeated measurements were performed in 20 patients after cardiac surgery. Pa and Pv equalized after 60 s of cuff inflation. For a single measurement, the coefficient error (CE) was 5% (± 2%) and the least significant change (LSC) was 14% (±5%). Averaging two measurements, the CE improves to 4% (±1%), and the LSC was reduced to 10% (±4%).

Maas et al. [81] compared these 3 methods in 11 postoperative cardiac surgery patients. Bland-Altman analysis for the difference between Pmsf-arm and Pmsf showed a bias of −1.0 (±3.1) mm Hg ($p = 0.06$) and a coefficient of variation (CV) of 15%. Although there was a non-significant bias, one may think that this is actually quite significant considering the small sample size of this study. Regarding the difference between Pmsf and Pmsa there was a bias of −6.0 (± 3.1) mm Hg ($p < 0.001$) and a CV of 17%. The three methods were useful to track changes after volume expansion.

The higher values of Pmsf observed in critically ill humans compared with the values reported from animal studies is still a focus of research. Repessé and colleagues [82] observed the Pmsf in 202 patients who died in the intensive care unit (ICU). The Pmsf was measured 1 min after the cardiac arrest, having disconnected the ventilator

and then recorded the equilibrium pressure in the arterial and/or central venous line. This was called "one-minute Pmsf," which had a mean value of 12.8 ± 5.6 mm Hg. Although the values reported in this study are closer to those previously described in animal models, the methodology proposed raised several questions. The cause of death and the process of dying was not described in this study. A critically ill patient may suffer a sudden cardiac arrest or may suffer a progressive deterioration that may take minutes or hours. By the time the heart stops, central nervous system hypoxia could be stabilized and a denervation process, with its consequences on the vascular tone, might be fully in place. This is crucial because the effect of an intact sympathetic system is essential to determine the real value of the Pmsf, as discussed earlier [9, 83, 84]. Given these limitations, the values reported in this study may not actually represent the real measurement of Pmsf. It should be viewed, instead, as an estimation of the Pmsf in patients with low vascular tone and no sympathetic activity. Therefore, the mean value reported cannot be compared with those reported in previous studies in humans with intact circulation [77, 80, 81].

Should the Venous Tone be Monitored at Bedside? Practical Implications

Despite the importance of venous tone on the maintenance of cardiovascular stability, there is still little evidence about the impact of this information on the management of critically ill patients.

Rangapa et al. [85] investigated the potential of a computerized decision-support system (Navigator™, Applied Physiology, Sidney, Australia) to improve consistency of hemodynamic evaluation and treatment decisions by ICU clinical staff with different levels of expertise and experience in 20 patients admitted after elective cardiac surgery. The study showed that Pmsa was commonly underestimated by all categories of ICU staff, and that this system may improve consistency in decision-making.

Sondergaard et al. [86] carried out a small pilot clinical trial in 27 postoperative patients requiring goal-directed therapy to evaluate the efficiency of the Navigator™ system in achieving hemodynamic targets (measuring the percentage time in target zone and the averaged standardized distance from the centre of the target [87] and time to achieve targets) and the level of concordance between the therapy suggested by the system and an expert clinician. The mean percentage time in the target zone was 36.7% for control and 36.5% for intervention, and the ASD was 1.5 in control and 1.6 in intervention (no p value was reported). There was a high level of concordance between decision support recommendation and anesthetist action (84.3%). The authors concluded that the treatment recommended by the Navigator system mirrored that of a senior anesthetist in the achievement of therapeutic goals. Unfortunately, this study is probably underpowered to show differences in the efficiency measurements, fluid balance, or vasoactive medications. In addition, it is quite interesting that in both cases the percentage of time in the target zone was so low.

In a small study, Yastrebov et al. [88] investigated the relationship between Pmsf-arm and echocardiographic variables of left ventricular filling such as left ventricular end diastolic area, volume and inferior vena cava (IVC) diameter in 13 healthy patients before surgery. Only a weak correlation was found between Pmsf-arm and the IVC diameter.

Some interesting studies demonstrated that some useful information could be obtained by observing the mean systemic filling pressure. The current consensus on circulatory shock and hemodynamic monitoring states that even in the context of fluid responsive patients fluid management should be carefully titrated, especially in the presence of elevated intravascular filling pressures [89]. However, a fluid challenge should increase Pmsf in order to challenge the cardiovascular system. Otherwise the test would not be valid. In a recent clinical trial [90], 80 patients after cardiac surgery were randomized to difference doses of crystalloids (from 1 to 4 mL/kg) infused over 5 min. Pmsf was measured with the arterial-venous occlusion method, and the effective dose was defined as the one that achieve and increase in Pmsf at least by 14% from baseline. In this study, 4 mL/kg was the dose that effectively increases Pmsf, and it was also found a significant difference in the proportion of fluid responders between the dose-groups: from 20% in the group of 1 ml/Kg to 65% in the group of 4 mL/kg.

In addition, a fluid challenge can be used not only to test fluid responsiveness but also, as spotted by Maas and colleagues [91], to assess systemic compliance. Given that Pmsf is the pressure at the pivot point, this may represent an estimation of the venous reservoir compliance. In this study, systemic compliance is reported from 15 postoperative cardiac surgery patients around 64 mL/mm Hg. Systemic venous compliance could be very useful information to prioritize treatment: A high compliance after a fluid challenge may indicate the use of vasopressors instead of infusion of a large amount of fluids. Another study [92] showed that administration of noradrenaline increased CO in preload responsive patients. Noradrenaline increased Pmsf either by reducing venous compliance or by venoconstriction (reduction of venous capacity and shifting unstressed volume to stressed compartment, see Fig. 8.2). Unfortunately, the authors did not assess the effect of noradrenaline on venous compliance. In the rest of the patients, noradrenaline had predominantly an arterial vasoconstrictive effect, increasing cardiac afterload. This study stressed the importance of monitoring venous tone and CO when using vasopressors.

Conclusion

The venous system plays an important role in the hemodynamic stability. Most of blood volume is stored and regulated in the venous territory by sympathetic reflexes that can modify the capacitance of the venous reservoir. The mean systemic filling pressure can be now measured and it is the pressure of the pivot point of the circulation, where the pressure is independent of blood flow. This pressure is the driving pressure of the venous return, and the reflexes that affect the venous reservoir affect Pmsf. Three methods have been described to measure Pmsf at bedside in

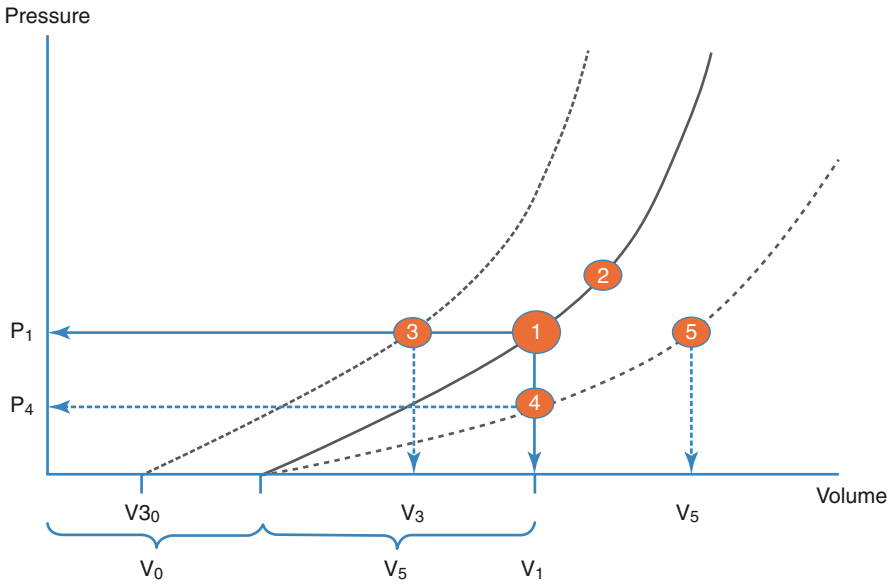

Fig. 8.2 Volume-pressure relationship in the venous compartment. The point 1 represents the total blood volume at the mean systemic filling pressure P1. For this point, the volume at 0 pressure is the unstressed volume (V_0) and the difference between the total volume (V1) and V_0 is the stress volume (V_s). The continuous black line represents the baseline compliance. The point 2 represents a change in pressure induced by a change in intravascular volume. When a certain amount of blood is removed from the venous system, point 1 can move forward. Point 3: the system now contains less blood (V3) at the same pressure given that some unstressed volume (now $V3_0$) was recruited into the stressed volume. However, the system can maintain the pressure-volume relationship (parallel dashed line). This means that the capacity of the system was reduced but not the compliance. When the system suffers an increased compliance, the same total volume is displaced from point 1 to point 4, as it is not able to generate the same amount of pressure (P4). To return to P1, volume must be expanded (V_5) unless compliance is corrected

patients with intact circulation. This variable can be now integrated to evaluate the intravascular filling status, to assess the efficacy of cardiovascular interventions and to explain the pathophysiology of the states of shock at the bedside.

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Restricted or Liberal Fluid Therapy

9

Thomas E. Woodcock

Abstract

While fluid deprivation and fluid overdose resulting from negligence or misinformed prescription are surely harmful, observations and experiments do not point to fluid therapy as a significant determinant of patient outcomes from major surgery. We can take steps to regulate (a) the extracellular fluid volume and (b) the intravascular—extravascular distribution of the extracellular fluid. On point (a), maintaining a positive input—output fluid balance of 1 to 2 liters on the day of surgery seems to be optimal for modern minimally-invasive surgery. On point (b) there are two interdependent extracellular fluid circulations, of blood and of interstitial fluid. The determinant of the equilibrium between plasma volume and interstitial volume are the transendothelial filtration rate (J_v) of fluid from the blood circulation to the interstitial circulation and the prenodal lymph flow rate (Q_{lymph}). Both are affected by anesthesia and by vasoactive agents. We can minimise post-operative edema (harmful interstitial fluid accumulation) and optimize intravascular fluid volume by taking steps to balance fluid input, fluid output, J_v and Q_{lymph}.

Key Points

1. A two-dimensional approach to perioperative fluid therapy manages the water volume balance and the plasma volume to interstitial fluid volume ratio.
2. Filtration rate (J_v) of fluid from the plasma to the interstitial fluid is a major determinant of the dynamic equilibrium between plasma volume and interstitial volume. It is affected by anesthesia and by vasoactive agents.

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3. Pre-nodal lymph flow rate (Q_{lymph}) is closely matched to J_v in health, and the way to optimize plasma volume to interstitial fluid volume ratio is to take steps to balance J_v and Q_{lymph}.
4. In hypovolemia, when microvascular pressures are low, spontaneous plasma volume refill is by protein-rich lymph *via* the efferent lymphatics and occurs at about 1 ml per minute. J_v is close to zero during hypovolaemia and so the colloid osmotic pressure of the resuscitation fluid has little effect on resuscitation volume.
5. Observation and research indicate that the red cell dilution efficiency of colloid solutions is up to five times that of crystalloids, but the resuscitative efficiency of colloids is only 1.5 times. Colloid-induced anemia and hypoalbuminemia in resuscitated patients is now well documented.
6. A false distinction is often made between situations in which capillaries are "leaky" as in sepsis, or non-leaky as in uncomplicated perioperative cases. This false distinction is used to legitimize peri-operative colloid use. In fact trauma, surgery, and sepsis are all associated with systemic inflammatory response, and there is no reason to distinguish them for the purposes of rational fluid prescribing.
7. New insights into non-osmotic sodium disposition probably explain the "Sodium Paradox" and the perioperative phenomenon of "Missing Sodium".
8. While hypotonic solutions may be safe and rational for the maintenance of fasted subjects, free water load cannot be cleared by arginine vasopressinemic perioperative patients whose renal collecting ducts are rendered permeable to water.

Introduction

It has long been supposed that there must be an optimal approach to fluid therapy for trauma and surgery that delivers lower complication rate and lower mortality. Too little puts the patient at risk of hypoperfusion, and too much leads to edema. Francis Moore was an early contributor to the scientific investigation of this hypothesis [1, 2]. His numerous studies in the 1950s and 1960s suggested that the stress of trauma and surgery caused salt and water retention, so that it is rational to restrict salt and water administration. Tom Shires measured a reduction in the effective extracellular fluid volume after major surgery, and attributed this to the development of an isolated "third space" of extracellular fluid due to paralytic ileus and edema at the site of injury [3]. He therefore proposed that it was rational to administer liberal amounts of isotonic salt solution to maintain the effective extracellular fluid volume [4, 5]. These opposing views so polarized the practices of surgeons and anesthetists that Moore and Shires published a plea for "Moderation" in the major surgical and anesthesia journals in 1967 [6].

Moore fully appreciated that there is a steady state, a dynamic equilibrium, between the volume of fluid in the interstitial phase and that found in the plasma. This partition of the extracellular fluid he expressed as the PV:IF ratio.[ref] The PV:IF ratio is around 0.23 in health, meaning that "one fifth of the entire extracullar volume is to be found in the plasma". Notice, however, that the concept of PV:IF

ratio is emphasised in Moore's commentary in order to highlight the fact that it is not a fixed ratio, it changes during hemorrhage, during spontaneous plasma refill, and during the infusion of intravenous fluids.

Writing in 1985, Twigley and Hillman expressed the view that contemporary perioperative fluid prescription was still predominantly driven by Shires' third space hypothesis and an understandable fear of renal failure and hyperkalemia [7]. They proposed the startlingly simple solution that blood and colloid solutions should be more used in order to preserve the blood volume and renal perfusion while restricting crystalloid infusion and so avoiding edema. Their "new approach to perioperative fluid administration" has been much repeated, with minor variations, in journals and textbooks by many of today's fluid therapy experts. It views the total body water as existing in three static compartments: (1) the plasma (with a suspension of red cells), (2) the interstitial space, and (3) the intercellular space. Infused colloid solutions are said to be restricted to the plasma by largely impermeable capillary walls, isotonic salt solutions are said to distribute through the plasma and interstitial compartments as far as the cell membrane, while free water dilutes all three compartments [8]. As we shall see, this paradigm is too simplistic. It does not explain what is observed in clinical practice and so cannot be used as the basis of a rational prescribing strategy. On the electrolyte front it ignores the fact that the volume of distribution of sodium is close to the total body water (the Sodium Paradox), making an isotonic salt solution an appropriate choice to treat pure dehydration [9]. On the colloid osmotic pressure front, it is incompatible with the Starling principle. Rodney Levick and Charles Michel explained some clinical corollaries of a revised Starling principle in 2010 [10]. Michel now prefers the term steady-state Starling principle. It was confirmed by experiments published in 2004, but had largely been ignored by clinicians and physiology teachers, though it held the key to explaining much clinical and experimental data that were otherwise inexplicable [11, 12]. The widely taught model of filtration–reabsorption balance does not occur in the microcirculation of most tissues. Tissue fluid balance depends on lymphatic function in most tissues [10].

My son and I offered a better paradigm, based on modern cardiovascular physiology. We called it the revised Starling equation and glycocalyx model (RSE&GM) [13]. It is a working paradigm for clinicians that explains the previously inexplicable: Why is 100 ml of isotonic salt solution as effective for resuscitation as 62–76 ml human albumin solution or 63–69 ml of a colloid solution [14, 15]? It explains why albumin bolus therapy is no more effective than isotonic salt solution in shock therapy, and why fluid boluses may be harmful [16, 17]. It explains why extravascular lung water may increase during fluid loading in the critically ill with presumed hypovolemia [18, 19].

An expert group writing in 2014 opined that "improved understanding of the endothelial glycocalyx has altered our comprehension of the role of colloid osmotic pressure in fluid balance" [20]. Since the first edition of this textbook the clinical relevance of the steady-state Starling principle has gained wider acceptance [21]. Nonetheless, more liberal approaches to fluid therapy, and a teaching that fluid overload and tissue edema are somehow inevitable during the early phase of critical

illness and in the perioperative phase of major surgery may still be harming patients. In the second edition of this chapter, I update the evidence supporting RSE&GM and examine other recent developments in fluid physiology.

The Michel–Weinbaum Model

The glycocalyx model, also known as the Michel–Weinbaum glycocalyx junction-break model of fluid exchange in a continuous capillary, is key to the new physiology. It is described by one of the men for whom it is named in Chap. 2. The microvascular permeability barrier of most capillary beds is revealed to function like a one-way valve that permits filtration but does not permit reabsorption (Fig. 9.1). At steady state filtration the counter-current diffusion of interstitial proteins is too slow to raise the subglycocalyx colloid osmotic pressure π_g which is therefore lower than the general interstitial colloid osmotic pressure π_i, creating a substantial plasma to subglycocalyx colloid osmotic pressure difference opposing

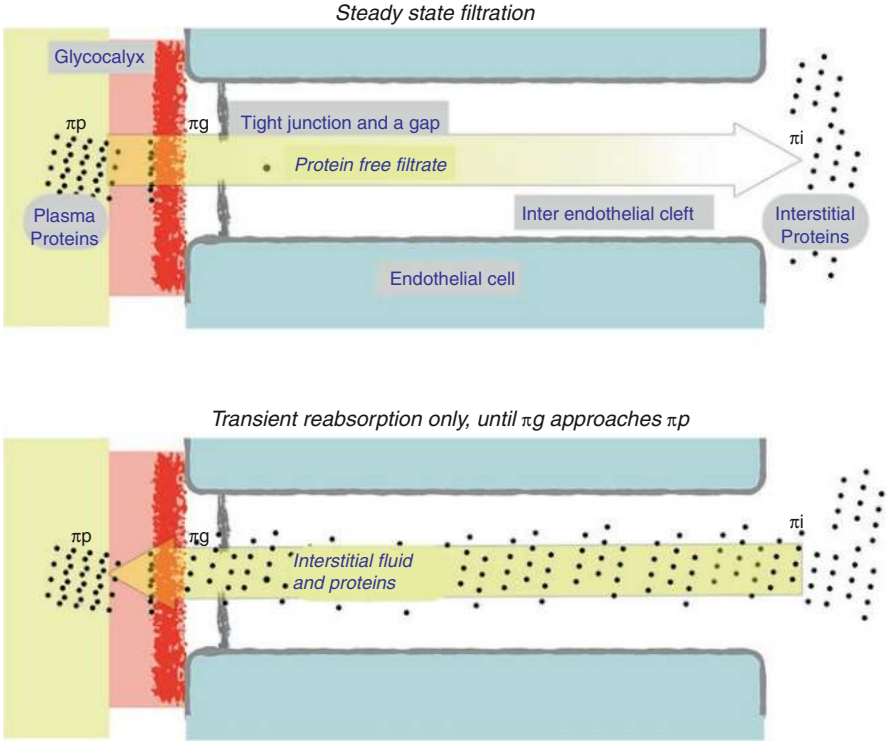

Fig. 9.1 A cartoon of solvent and protein movement through an interendothelial cleft during filtration (above) and transient reabsorption (below). The concentration of proteins (shown as dots) is very low in the subglycocalyx space during filtration and contributes to a very high colloid osmotic pressure difference across the glycocalyx which normally opposes filtration

the filtration rate. When capillary pressure falls low enough for reabsorption to begin, diffusion of interstitial proteins to the subglycocalyx space wipes out the colloid osmotic pressure difference that was driving reabsorption and a new steady state of minimal filtration is established. Notice that the endothelial surface layer that excludes red blood cells has two phases, with intravascular albumin molecules concentrated at the interface between the membrane-bound glycocalyx matrix and the outer surface layer.

The Revised Starling Equation and Glycocalyx Model (RSE&GM) Paradigm

The revised Starling equation and Glycocalyx model (RSE&GM) paradigm is founded on clinical experiments by Robert Hahn who showed that the rapid infusion of an isotonic salt solution brings about a change in red blood cell dilution that can be explained by a two-compartment volume kinetic model [22–24]. There is an initial central volume of distribution for the infused fluid and a subsequent distribution to a peripheral or tissue volume. The infusion has measurable effects on transendothelial filtration, lymph flow and urine output which appear to depend on the rate of infusion [24] (Fig. 9.2). Hahn reports that colloid solution boluses have a more profound and prolonged effect on red cell dilution, making a single compartment model adequate for describing the kinetics of the acute volume disequilibrium. That is not to say, however, that colloid therapy has no effect on transendothelial filtration and lymph flow.

RSE & GM emphasizes volume kinetics. RSE&GM brings several new physiological concepts to the fluid debate, which help to explain why colloids are of little benefit for resuscitation from hypovolemia. It is important to remember that I am here presenting a clinician's simplified approximation of the relevant physiology. I provide a comprehensive account of modern fluid physiology for clinicians in a recent textbook [25].

Heterogeneity of the Microvasculature

Fluid therapy teaching often overlooks the heterogeneity of capillaries and venules. The human microvasculature is composed of four very different types of capillaries, whose distinct functions must be appreciated:

1. The 1.5 kg liver takes around 1 ml/min of the healthy cardiac output/gram of tissue. Like the spleen and bone marrow, it has "sinusoidal" capillaries, which have an incomplete glycocalyx and are freely permeable to larger molecules, making the interstitial fluid of these tissues an extension of the plasma volume. It creates about 50% of the total lymphatic flow to the thoracic duct. In resuscitated septic shock patients, as much as 50% of the cardiac output goes to this very leaky microcirculation.

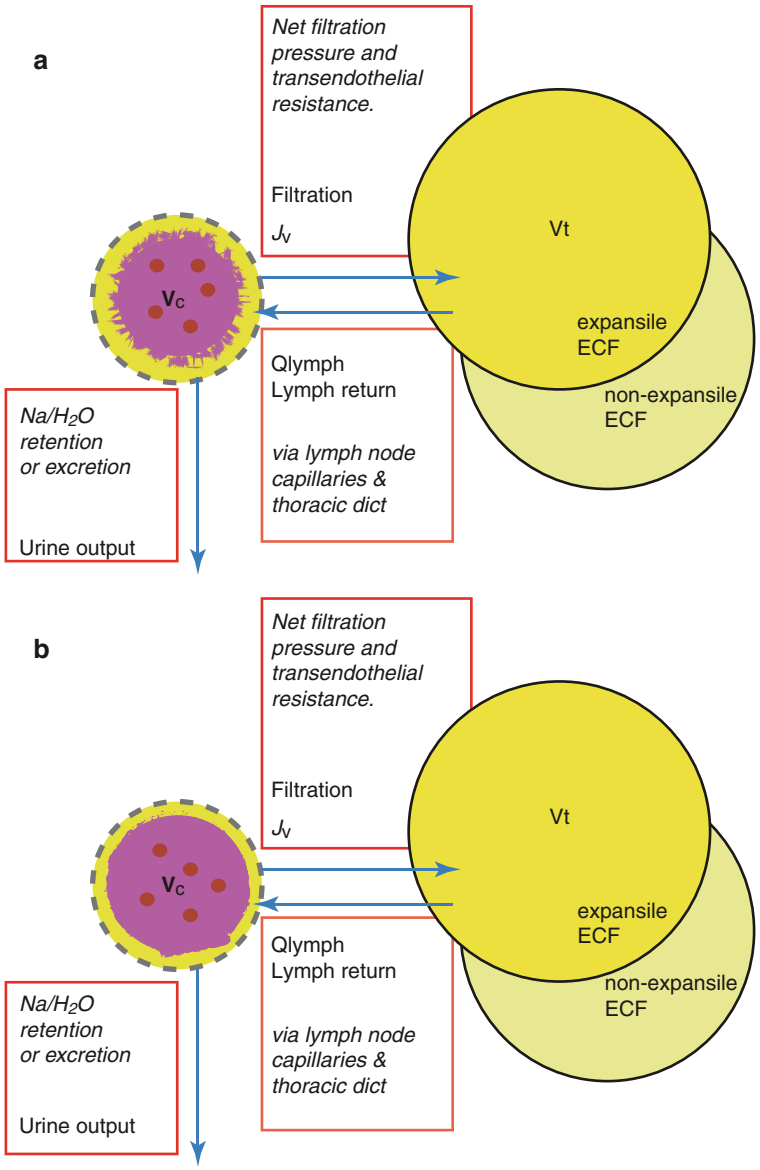

Fig. 9.2 A kinetic diagram of extracellular fluid distribution. Gel phase of the central and tissue volumes indicated by yellow, free-flowing plasma of the central volume indicated by pink. Erythrocyte volume indicated by red disks. (**a**) Shows a healthy intravascular gel phase (the endothelial glycocalyx and outer surface layer). (**b**) Notice how dehydration or fragmentation of the endothelial glycocalyx layer leads to erythrocyte dilution. When induced by colloid infusion, this dilutional anemia is frequently but erroneously stated to prove that colloids are superior plasma volume expanders

2. The highly specialized renal glomerular capillaries are continuous but feature open fenestrations for the filtration of fluid to the renal tubules (the glomerular filtration rate [GFR]). They operate at a high capillary pressure and never absorb fluid.
3. Diaphragm-fenestrated capillaries operate at lower capillary pressures and are specialized to absorb fluid from interstitium to plasma when needed. They are found in absorbing tissues such as the intestinal mucosa, the endocrine glands, lymph nodes, and renal peritubular capillaries.
4. The greatest number of systemic and pulmonary capillaries are nonsinusoidal, nonfenestrated capillaries and feature a continuous endothelial surface layer that sparingly filters fluid via occasional gaps in interendothelial cell junctions to the interstitium of their tissues, including connective tissues, lung parenchyma, and brain. The endothelial surface layer is now appreciated to have two phases. The membrane-bound glycocalyx molecules support a more fluid outer zone which features long strands of hyaluronan. The Michel–Weinbaum glycocalyx junction-break model proposes that effective pore size (small or large) in such capillaries is a function of the spaces between the matrix fibers of the glycocalyx, while the area for fluid exchange is a function of the length of the slit-like junction breaks between adjacent endothelial cells. In the capillaries of the brain and spinal cord, endothelial cell membranes are tightly opposed by zona occludens tight junctions with few breaks, resulting in very small effective pore size of barely 1 nm. Their integrity is reinforced by the presence of adjacent interstitial pericytes (microglia). The blood–brain barrier is therefore only permeable to the smallest non-lipid-soluble molecules. Nonsinusoidal, nonfenestrated capillaries of muscles, connective tissues, and lungs have macula occludens loose junctions to their intercellular clefts, and the effective pore size there is up to 5 nm, making them permeable to molecules as large as myoglobin.

Now consider the endothelial surface layer in these capillaries. It is easily compressed in volume by almost anything we do to our patients, releasing glycosaminoglycans (GAGs) into the circulating plasma. Albumin molecules are entrapped and retained at the interface between the glycocalyx and its outer layer, in part by electrostatic means, restricting their free passage through it, and so, behaving as an imperfect filter. Inflammation damages the glycocalyx and, so, reduces the reflection coefficient sigma for albumin, with glycocalyx components including the GAGs appearing in blood samples. Staverman's reflection coefficient sigma is an index of the effective, as opposed to measured, colloid osmotic pressure effect on transendothelial solvent filtration (J_v). As such, a reduced sigma limits the colloid osmotic pressure opposition to J_v and gives free rein to the hydrostatic pressure filtration driver. However, even when sigma approaches zero, the resistance to fluid filtration caused by the basal membrane and extracellular matrix gel remains substantial. The tissues that can accumulate substantial amounts of interstitial fluid after trauma and sepsis (i.e, the more compliant tissues) are loose connective tissues, muscles, lungs, and gastrointestinal mesentery and mucosa. For example,

extravascular lung water measured by double-indicator dilution can increase from around 500 ml to 2.5 l in pulmonary edema, while the loose connective tissues and muscles can expand to many liters of peripheral edema.

Hahn's Volume Kinetics

Robert Hahn's series of experiments on the volume kinetics of rapidly infused intravenous (IV) fluids measured the hemoglobin concentration of arterial or venous blood and modeled a central and a tissue volume that broadly represents the intravascular and extravascular fluid volumes, respectively. The peripheral volume is found to be 6–8 l, less than the anatomic interstitial fluid volume. As volume kinetics measure only the volume that can be expanded, this will therefore not include spaces limited by rigid structures such as the bone (brain, marrow) or fibrous capsules (liver, spleen, kidney) (Fig. 9.1). This goes some way to explaining why isotonic salt solutions are more efficient plasma expanders than we might expect if we were to presume their distribution throughout the total body water. In systemic capillary leak syndrome, so much fluid goes to the soft tissues of the limbs that it can cause compartment syndromes.

Three Intravascular Fluid Volumes

For the purposes of the RSE&GM paradigm, there are three intravascular fluid volumes. The first two, plasma volume and red cell volume, which make up the circulating blood volume, are well known. The third is the noncirculating intravascular volume occupied by the endothelial surface layer which includes the membrane-bound glycocalyx molecules that create a fiber matrix scaffold). Being on average about two microns thick, the fragile endothelial surface layer can account for as much as 1.5 l of the intravascular volume in health. As it excludes red cells, acute reductions in the thickness (and so volume) will increase the volume available to red cells and lead to a reduction in the hematocrit. GAGs are typically shed to the circulation when the glycocalyx is thinned.

A key concept of the new paradigm is that a bolus of an isosmotic plasma substitute has a central volume of distribution that approximates the free-flowing plasma, while a bolus of an isotonic salt solution has a central volume of distribution that includes the intravascular gel phase and approximates the whole of the intravascular volume, and possibly the interstitial space of the sinusoidal tissues. The concept is supported by consistent clinical reports that adequate resuscitation with an isosmotic plasma substitute can be achieved with slightly smaller volumes than adequate resuscitation with a crystalloid, but at the expense of much diluted hematocrit. The ability of plasma and plasma substitutes to cause anemia is still widely misinterpreted as indicating that the colloids are "better volume expanders." In volunteers

and anesthetized patients, the *volume effect ratio crystalloid to colloid for causing anemia and hypoalbuminemia* is about 4:1 or 5:1. In the misleading words of researchers in Munich, "The intravascular volume effect of Ringer's lactate is below 20%" [26]. However, in septic patients, in nonseptic intensive care patients, and in surgical patients undergoing goal-directed fluid therapy, the *volume effect ratio crystalloid to colloid for correction of hypovolemia* is only about 1.5:1. The data of Jacob et al. [26] show that a crystalloid infusion at three times the rate of blood withdrawal perfectly preserves hemodynamic stability; in other words, they could have concluded that for hemodynamic purposes "the intravascular volume effect of Ringer's lactate is greater than 33%". Erythrocyte or albumin dilution data were wrongly presumed to indicate resuscitative effectiveness.

Biophysical Osmotherapy Causes Haemodilution

It has long been known that plasma volume refill after haemorrhage or withdrawal of blood occurs at a rate of about 1 ml per minute and is achieved without a reduction in plasma protein concentration. Most of this autoresuscitation fluid comes from pumped mesenteric lymphatics and the thoracic duct, and is called "the essentiality of the lymphatic system to the recovery from shock" [27–30].

To investigate if edema fluid can be mobilised from the tissues to the blood and excreted as urine, researchers at the Karolinska Institute recently investigated the hemodilution that follows an acute increase in the plasma colloid osmotic pressure in fifteen healthy euvolaemic volunteers. Using a hyperosmotic human albumin solution they increased the plasma colloid osmotic pressure by about 8%, the plasma albumin concentration by about 16% and found that the volume of distribution of red blood cells (their surrogate for plasma volume) was transiently increased by about 16%. Maximal haemodilution was reached within 20 min post-infusion but was then halved by 4 h [31]. Red cell dilution studies of hyperoncotic human albumin solution transfusion in critically-ill patients have also been interpreted as showing osmotic absorption of fluid from the extravascular to intravascular compartment, but without information from an indicator of the whole intravascular volume, such as Dextran 40, such a conclusion is not justified. To cause an acute increase in circulating plasma colloid osmotic pressure is to cause a disequilibrium event that first draws water from the non-circulating gel phase of the intravascular volume associated with the glycocalyx and the interstitial fluid of the liver. The steady-state that follows is of greater importance but is too often overlooked.

After a century of the classic Starling principle, which suggests filtration at the arteriolar portion of a capillary and reabsorption at the venular end, it can be hard to accept the slightly more complex reality and to grasp the consequences that inform RSE&GM. With the exception of the diaphragm-fenestrated capillaries that can absorb solutes at normal capillary pressure, reabsorption of fluid from interstitium to plasma does not occur, even at reduced capillary pressure. The mechanism is the

Michel–Weinbaum glycocalyx junction-break model, which preserves a state of minimal filtration even when the hydrostatic transendothelial pressure difference delta P is low. Intravenous colloid therapy cannot promote absorption and cannot help to prevent or treat interstitial edema.

The J-Curve and the J-Point

As a consequence of the Michel–Weinbaum glycocalyx junction-break model, a plot of the transendothelial solvent filtration rate J_v against capillary pressure based on the steady-state Starling principle demonstrates that J_v remains close to zero with rising capillary pressure until the convection current of filtrate through the interendothelial channels is sufficient to bring the sub-glycocalyx-protected region's colloid osmotic pressure π_g close to zero. The transendothelial colloid osmotic pressure difference delta π is then maximal, and further increases in delta P will widen the difference between delta P and the now-fixed delta π, causing a sharp rise in J_v. This creates an inflection on the curve that makes it appear *J*-shaped (Fig. 9.3). The inflection is called the *J*-point [13]. Charles Michel in this textbook describes this curve as a hockey stick curve.

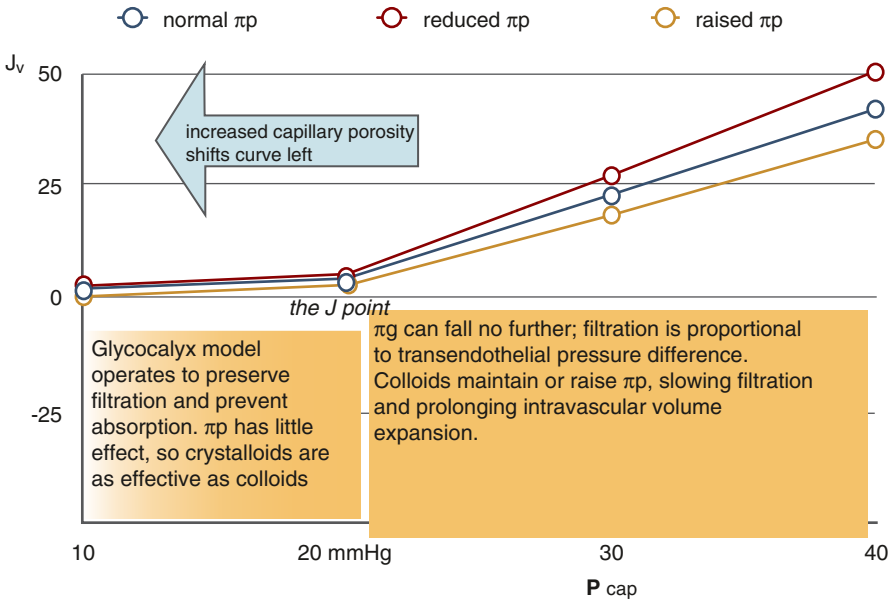

Fig. 9.3 The *J*-curve. A plot of the transendothelial solvent filtration rate J_v against the capillary pressure P_{cap}. In health, capillary pressure is regulated around the J-point. Raising the colloid osmotic pressure of plasma π_p only increases the transendothelial colloid osmotic pressure difference delta π when capillary pressure is higher than normal (heart failure or fluid overload) and the sub-glycocalyx colloid osmotic pressure π_g is close to zero. Around and below the *J*-point (health and hypovolemia), J_v is low and essentially uninfluenced by π_p

Manipulating Capillary Pressure

One of the first consequences of inflammation is a fall in the interstitial pressure as integrins change the conformation and hydration of structural collagen fibers. J_v therefore increases, beginning the shift of extracellular fluid balance from the intravascular to the extravascular compartment. Precapillary vasodilation follows and increases the capillary pressure and so further increases J_v. If the hemodynamic reflexes are working, blood pressure is maintained by increased cardiac output (capillary recruitment), which is another factor increasing J_v in the early phase of systemic inflammation.

A focus on capillary pressure brings a new perspective on the role of low-dose arteriolar pressor therapy in anesthesia and intensive care practice. Typically, the goal of pressor therapy is to maintain an adequate systolic arterial pressure after adequate resuscitation of the intravascular volume and stroke volume, allowing more restrictive use of fluids. In terms of the RSE&GM, arteriolar pressors are expected to raise diastolic arterial pressure but lower capillary pressure and so reduce J_v, keeping more of the extracellular volume intravascular. Now we can see alpha-1 agonists as part of a potential anti-edema strategy. They have even been found to increase urine output, but I do not think it is helpful to describe this as a diuretic effect. Notice that in vasodilated contexts, such as sepsis or anesthesia [32], capillary filling pressure is close to the arterial diastolic pressure. There is a case for paying more attention to diastolic pressure in perioperative care [33, 34].

Concern that capillary hypertension is injurious will make us more cautious about employing rapid boluses as a way to increase diastolic pressure. RSE&GM predicts transiently high capillary pressures during rapid transfusion, which will cause excessively raised J_v, reducing the intravascular contribution of whatever resuscitation fluid we choose. A slower infusion rate will cause lower capillary pressure peaks, minimizing hyperfiltration and maximizing efficient resuscitation of the intravascular volume. Robert Hahn has produced human data that confirm the prediction, but he attributes the phenomenon to the visco-elastic properties of the interstitial matrix. If we infuse fluids at lower rates, edema is avoided and the central fluid volume is better conserved.

Focusing on capillary pressure through the RSE&GM paradigm reveals a need to understand the transendothelial resistance to fluid flux (represented in the Starling equation as its reciprocal, the hydraulic conductance L_p). The glycocalyx is the first and the major fiber matrix resistor in the current of fluid and solutes between plasma and lymph. The basement membrane and extracellular matrix are the second and third resistances in a series.

The basement membrane, where it exists, is a specialized part of the extracellular matrix 60–100 nm in thickness, composed of type IV collagen and laminin and closely adherent to the cell membrane. The collagen matrix can be thought of as a special phase of the extracellular fluid, which provides an exchangeable sodium store (around 400 mmol/l, compared to about 145 mmol/in general interstitial fluid) [35, 36]. Bhave and Neilson propose that short-term sodium storage and interstitial volume homeostasis may be relevant to transient or disequilibrium phenomena such

as blood pressure dipping, flash pulmonary edema, rapid blood loss, burns, and sepsis [37]. It may be a mechanism that enables hypertonic sodium resuscitation to be effective without edema or hypernatremia.

Collagen fibrils also occur within the interstitial space, upon which glycoproteins such as fibronectin and proteoglycans (protein molecules with GAG side chains) are arranged, and contain free GAGs. Toll-like receptors are found within the extracellular matrix and are believed to have a pivotal role in the early development of systemic inflammatory response and ventilator-induced lung injury. Integrins and their receptors modulate cell locomotion through the extracellular matrix, and it has been discovered that they can modulate interstitial pressure by bringing about conformational changes to collagen that allow the GAGs to become hydrated. An acute reduction in interstitial pressure occurs in inflammatory conditions, increasing delta-P and thereby increasing J_v by as much as 20-fold independently of other causes of capillary "leak." Changes that compact the glycocalyx releasing GAGs into the circulating plasma are associated with increased transendothelial protein flux, but compaction of the glycocalyx and increased porosity may be separate processes and the association may not be entirely causal. Although transfused macromolecules do not easily permeate an intact endothelial glycocalyx layer, they pass easily into the interstitial fluid of the sinusoidal capillaries in the bone marrow, spleen, and liver, equilibrating with interstitial macromolecules and returning to the venous system via lymphatics. An increase in the proportion of the cardiac output going to sinusoidal tissues will increase overall J_v and the transcapillary escape rate of albumin.

Understanding "Leaky Capillaries"

Many of the clinical challenges of anesthesia and critical care are attributed to what we often call "leaky capillaries." Pushed to elaborate, even the experts may recall the reflection coefficient but few can elaborate further. The equations we are told are Starling's were in fact proposed many years after his death. The most frequently cited equation explains the transendothelial solvent filtration rate J_v in terms that describe the net hydrostatic pressure difference and net colloid osmotic pressure difference across the semipermeable microcirculation. The reflection coefficient sigma modifies the apparent delta π to the effective delta π. Histamine and other autocoids are known to increase the length and number of intercellular junction breaks, especially in the distal part of the capillary and the venules. The surface area for filtration within each capillary and the hydraulic conductivity L_p are thereby increased and increase the J_v. Note that in some versions of the Starling equation for J_v, the product of surface area and hydraulic conductivity is called the filtration coefficient K_{fc}.

Less often taught, but equally important to understanding the pathophysiology, is the equation explaining a transendothelial solute transfer rate J_s as the sum of the mass of that solute carried with the transendothelial filtrate (convection) and the mass of that solute that permeates the microcirculation independently of flow

(diffusion). In clinical considerations the solute of interest is albumin. Researchers who measure J_s of albumin or another marker molecule in disease states often presume that J_v will be increased with J_s and cause edema. Permeability as it appears in the equation for J_s is an index of how readily albumin appears to diffuse across a capillary if it were a simple semipermeable membrane dividing static fluid spaces. It is not. Albumin is actively transported across continuous capillaries via a membrane-associated protein that has been called gp60 or PV-1 and is now referred to as caveolin. Caveolin deficiency is incompatible with life. The rate of transfer of albumin, and other proteins having their own transport system, to the interstitium will appear to be a change in the number of large pores. Plasmalemmal vesicles (caveolae) carry some water with the albumin, but the convective interendothelial pathways predominate. Places where the fibrematrix covering a junction break is thinned will also behave like more large pores.

Curry and Adamson have reviewed understanding of the tonic regulation of vascular permeability in health and disease [38]. Sphingosine-1-phosphate is synthesized in erythrocytes and transported to the endothelium by albumin. It modulates

- the adherens junction,
- continuity of tight junction strands,
- and the synthesis and degradation of glycocalyx components.

Baseline permeability appears to be maintained by the small GTPase enzymes called Rap1 and Rac1, which are dependent upon the supply of sphyngosine-1-phosphate. Inflammatory stimuli act to reduce Rac1 and Rap1 activity, and so enhanced delivery of sphyngosine-1-phosphate should be able to buffer inflammatory harm. This knowledge suggests it is important to maintain erythrocyte and endogenous albumin delivery to the vascular endothelium and should make us even more concerned about the use of plasma substitutes that cause anemia and hypoalbuminemia.

The Circulation of Tissue Fluid to Lymphatic Vessels and Return to the Intravascular Space

RSE&GM recognizes that the microvasculature is not a passive biophysical barrier separating the vascular and interstitial compartments of the extracellular fluid's circulation. The collecting (afferent) lymph vessels have barrier properties comparable to the venules and carry filtered tissue fluid to the lymph nodes whose capillaries are diaphragm-fenestrated and capable of fluid absorption. As much as 50% of the fluid arriving at a lymph node is reabsorbed there, so the lymph in the efferent lymphatics has a high protein concentration and is pumped to the thoracic duct. It is thought that most of the efferent lymph re-enters the venous system via the thoracic duct, but other lymphatic–venous collaterals can be recruited if the duct is tied off. Radiation ablation of lymph nodes predisposes to edema, a clear practical demonstration that nonfenestrated capillaries outside the lymph nodes are not capable of significant

absorption of tissue fluid. The spontaneous contractility of the lymphatics is enhanced by alpha adrenergic agents and suppressed by inflammatory mediators and opioids. It is worth recalling that 25% of the cardiac output goes to the discontinuous capillary circulations of the liver, spleen, and bone marrow, where sigma for albumin and any other large molecule is very low, and that more than 50% of the high-protein lymph in the thoracic duct originates from the liver. In resuscitated hyperdynamic sepsis, the proportion of blood going to the liver rises to as much as 50% so that higher-molecular-weight molecules will be easily lost from the bloodstream.

Missing Sodium

It is widely appreciated that renal sodium reabsorption under the influence of aldosterone occurs in the distal convoluted tubules and maintains both extracellular fluid volume and osmolarity. Excess sodium intake drives up extracellular fluid volume with adverse consequences. Fluid and electrolyte balance studies on perioperative patients reveal a rather more complex state of affairs. The volume of distribution of sodium within the body is much larger than the extracellular fluid volume. Surgical patients often acquire a substantial sodium load without the associated water retention (edema) we would expect from the osmolar balance—this has been called "missing sodium". This non-osmolar sodium appears to be stored within the gel phase of the interstitium, and especially the interstitium of skin and connective tissues, as sodium hyaluronan. Non-osmolar sodium is therefore in an equilibrium with osmolar sodium ions and is being shown to have a physiological role in fine-tuning the extracellular fluid volume while sodium balance fluctuates. Moreover, longer term sodium loading leads to increased density of interstitial lymphatic channels which are the active interface between the stored and the circulating sodium. It has often been taught that excess sodium intfusion inevitably leads to edema, but the non-ionic non-edematous storage of excess sodium in surgical patients was first observed in 1986 [39]. The clinical importance of this second sodium store is emerging.

Intracellular Fluid Volume Is Regulated Independently of Total Body Water

A parallel phenomenon is the maintenance of intracellular fluid volume over a range of body water osmolarities. In a cohort study of post-surgical patients treated in an Intensive Care Unit with conventional intravenous fluids for 4 days, Hessels and colleagues found that there was a strongly positive accumulation of sodium and total fluid, but a negative balance of electrolyte-free water and potassium. In a substudy comparing the effects of a prescribing potassium to a target of [4.0 mmol l^{-1}] or [4.5 mmol l^{-1}] they found that all the excess potassium of the second group was renally excreted. They reasonably interpreted these observations as showing that

excess fluid in clinical practice results in interstitial expansion (extracellular edema) while the intracellular volume, where potassium is the dominant osmolar cation, is regulated close to its healthy normal. They speculate that the cytosol is able to clear alternative osmolytes when there is volume increase by electrolyte free water infusion, and generate alternative osmolytes when hypertonic saline infusion reduces cell volume. Intracellular volume is thereby conserved in the face of changing body water tonicity [40, 41].

A Revised Twigley–Hillman Diagram

The Twigley–Hillman diagram represents the total body water in three static compartments divided by two barriers [7, 8]. I have offered an improved 2-compartment volume kinetic representation of extracellular fluid to assist rational fluid prescription. The volume of the third compartment, intracellular fluid, remains remarkably constant with fluctuations in the extracellular fluid volume [40, 41]. I suggest a revised Twigley–Hillman diagram of the total body water. From left to right, it represents:

- Plasma. The free-flowing intravascular plasma volume. Normally around 3 l of the 4 l intravascular fluid.
- Red blood cell volume (intracellular fluid) of approximately 2 l is not shown separately on this diagram.
- Endothelial surface layer (ESL). Circulating erythrocytes are repelled by the outermost, rather porous gel phase of the endothelial surface layer while the inner fibre matrix of the membrane-bound glycocalyx performs the small pore function of excluding larger molecules, including albumin. It is impossible to attribute a precise volume to this phase, but about 1 l in health.
- Aqueous and gel fluid phases of the triphasic interstitium are distinguished. In health the aqueous phase may be a little as 1%, but increases greatly in oedema. The third phase is structural, mostly collagen Type I fibres, which appear to channel the interstitial flow of solvent and solutes. Sodium hyaluronan is a non-osmotic buffer of sodium ions in the gel phase, and albumin is excluded.
- Lymph is aqueous interstitial fluid that has entered the lymphatic vasculature.
- Intracellular fluid.

The revised Twigley–Hillman diagram (Fig. 9.4) of total body water compartmentalisation emphasises the extracellular fluid (ECF) circulation (blue arrows) which occurs in most tissues most of the time. The intravascular space normally contains about 5 litres of blood and 1 litre endothelial surface layer from which circulating red blood cells are excluded. The intravascular extracellular fluid is free-flowing aqueous (plasma) and gel phase (ESL). ESL contains the fibre matrix molecules of glycocalyx which arise from the endothelial cell surface. The triphasic interstitial space has a structural collagen fibrous phase and around 14 litres of fluid; an aqueous phase, a gel phase within which glycosaminoglycans such as hyaluronic

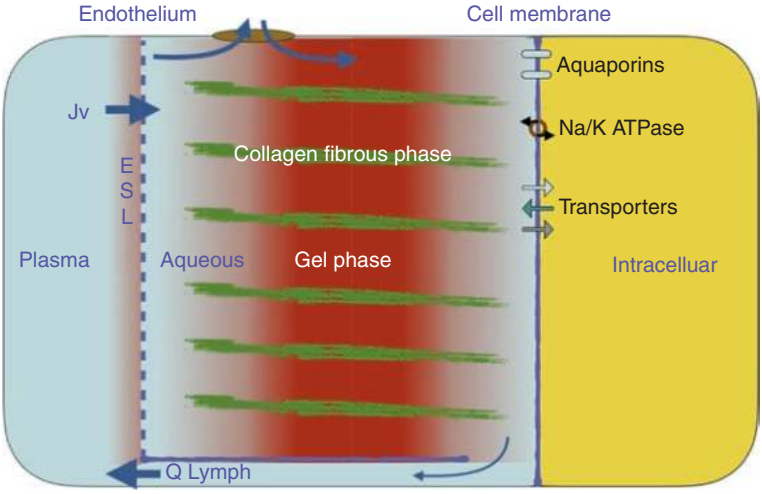

Fig. 9.4 A revised Twigley–Hillman diagram. J_v is the transendothelial solvent filtration rate which at steady state is balanced by the lymphatic return of solvent Q_{lymph} *via* capillary absorption within lymph nodes and as efferent lymph

acid have the capacity to store sodium without raising tissue osmolality, and lymph. The intracellular fluid (ICF) volume, normally about 23 litres, is sensitive to acute changes in ECF osmolality. However, cell volume regulatory mechanisms exist to preserve the steady-state intracellular fluid volume and enable subjects to tolerate chronic hypotonicity.

Water and solutes enter and leave the body across epithelial barriers, represented here by a brown ellipsoid. In clinical practice we can infuse fluids directly into, or haemofilter water out of the free-flowing plasma.

In Sinusoidal tissues (liver, spleen and bone marrow) the ESL is discontinuous and there are windows (fenestrations) through the endothelium that exclude red blood cells but admit albumin to the interstitial space so that there is no trans-endothelial colloid osmotic pressure difference to oppose filtration.

In Non-sinusoidal tissues the continuous ESL is almost impermeable to albumin so that filtered fluid in the immediate sub-glycocalyx space (protected region) has a very low colloid osmotic pressure compared to plasma or the general interstitial fluid. The trans-endothelial colloid osmotic pressure difference opposing filtration is therefore high. Michel and Weinbaum correctly hypothesised that if transendothelial water movement across non-sinusoidal capillaries and venules is transiently reversed by a sudden drop in the hydrostatic pressure difference, interstitial albumin rapidly enters the protected region, diminishing the trans-endothelial colloid osmotic pressure difference. The net water movement therefore quickly return to steady-state filtration. This is the Michel–Weinbaum No Reabsorption Rule.

Water is absorbed from afferent lymph into lymph node capillaries and venules. Efferent lymph therefore has high protein and lipid content and returns to the central

veins *via* the thoracic duct. Acceleration of protein-rich efferent lymph to the circulating blood volume is an important compensatory response to haemorrhagic shock in humans.

Exceptions to the No Steady State Absorption Rule: Hypodermoclysis

In 1896 Ernest Starling performed experiments on small dogs (typically 6–12 kg in weight) in which he infused 1% sodium chloride solution into the connective tissues of the back leg and observed that this fluid was absorbed into the blood stream by capillaries [42]. He wrote;

> The importance of these measurements lies in the fact that, although the osmotic pressure of the proteids of the plasma is so insignificant, it is of an order of magnitude comparable to that of the capillary pressures; and whereas capillary pressure determines transudation, the osmotic pressure of the proteids of the serum determines absorption.

This science is still emphasised in undergraduate medical education and in postgraduate critical care teaching, but Starling himself added some caveats. Firstly, he appreciated that the effect was transient and would lead to a no-absorption steady state;

> With diminished capillary pressure there will be an osmotic absorption of salt solution from the extravascular fluid, until this becomes richer in proteids; and the difference between its (proteid) osmotic pressure and that of the intravascular plasma is equal to the diminished capillary pressure.

Secondly, he appreciated that the effect he observed with exogenous saline may not be applicable to what he called dropsical fluid reabsorption;

> Salt solutions, isotonic with the blood-plasma, can be and are absorbed directly by the blood vesels. This statement probably holds good for dropsical fluids containing small percentages of proteids.

A century on the only fault that we can find in Starling's interpretation of his experiments is that he did not entirely appreciate the importance of the fact that the interstitial proteid concentration is dynamically determined by the rate of solute influx, J_s, relative to the rate of water influx J_v. The design of his experiment uncoupled the physiological inverse 'extravascular dilution' relationship between or π_i and J_v, and created an exceptional condition that has misled colloid osmotic pressure therapists ever since.

To this day the subcutaneous route is known to be safe and effective for the administration of isotonic solutions and certain drugs. Indeed, the complication rate is less than with intravenous administration. Hypodermoclysis is widely used in smaller animal veterinary practice, but in an adult human two litres per

day is achievable, enough for what is called ‘maintenance’ therapy while enteral nutrition and hydration are suspended. The rate of absorption can be increased by adding hyaluronidase, an enzyme that increases the area for absorption of fluids and drugs. Hypodermoclysis with intravenous fluids brings about the same electrolyte measurements or osmolalities as intravenous infusion at the same rate. Animal studies have shown equivalent subcutaneous absorption of cephalosporins and clindamycin when compared with intravenous absorption. Studies with radioisotope tracers in humans have shown that clearance from subcutaneous tissue is complete within an hour after the termination of the subcutaneous infusion [43].

Recall that fluid filtered by the glycocalyx layer is almost protein-free and creates a low colloid osmotic pressure “microdomain” at the interendothelial cleft exit. However, if filtration slows, tissue proteins almost immediately diffuse back into the cleft, raising the colloid osmotic pressure, diminishing the colloid osmotic pressure difference, and preserving a low rate of filtration. In the case of injected protein-free isotonic salt solution, the volume of the low colloid osmotic pressure domain at adjacent cleft exits is relatively immense, and there is no available protein to diffuse back into the cleft. Absorption can therefore occur until the injected volume has been taken up and tissue proteins can again enter the cleft, restoring the normal equilibrium of low filtration.

Exceptions to the ‘No Steady-State Absorption’ Rule: Effect of Local Epithelial Transport

There are of course situations where absorption of fluid from the interstitium to the plasma is physiologically vital.

- The peritubular capillaries of the renal cortex and the ascending vasa recta of the renal medulla are in a continuous state of absorption of interstitial fluid which is continuously secreted by renal tubular epithelium.
- The renal collecting ducts supply protein-free solvent and solutes to the medullary interstitium to keep the colloid osmotic pressure low enough for continuous absorption of fluid by the medullary capillaries. Convective solvent flow even carries interstitial albumin molecules back into the renal veins. There are no lymphatic channels in the renal medulla.
- While the intestine is absorbing enteral water the mucosal epithelium secretes water into the interstitium for absorption by mucosal capillaries.
- In lymph nodes interstitial fluid is continuously replenished by the flow of prenodal lymph with a low protein concentration.
- At the blood-brain barrier the perivascular pool of aquaporin 4 channels in pericytes (astroglial cells) delivers water to the abluminal side of the endothelium. At the same time cerebrospinal fluid is being delivered by the glymphatic system to the aquaporin-4 channels of astroglial cell foot processes so that it can join the brain interstitial fluid.

In each case the renewal of interstitial fluid from an adjacent epithelial secretion of low protein concentration uncouples the inverse 'extravascular dilution' relationship between π_i and J_v, and prevents π_i from approaching π_p. The colloid osmotic pressure difference supporting absorption of interstitial fluid to the plasma is protected.

Exceptions to the 'No Steady-State Absorption' Rule: Discontinuous Capillaries of the Sinusoidal Tissues

There is almost no hydrostatic pressure gradient or colloid osmotic pressure gradient being exerted across the fenestrated endothelial cells of the space of Disse, the hepatic version of interstitial space. It is freely connected to the intravascular space and so solvent and solutes may freely pass in either direction. Indeed, if the purpose of a lymphatic system is to circulate interstitial proteins and larger molecules from intestitium to plasma, one might question whether the liver needs a lymphatic system at all. It has long been appreciated that fluid infused into bone marrow equilibrates very rapidly with the plasma volume, without having to go *via* lymphatics.

Scientific Method in Peri-operative Fluid Therapy Research

In the first edition of this Chapter I pointed out that the great philosopher Ludwig Wittgenstein was very critical of the Scientific Method as applied to investigation of the condition called shock back in 1943 [44, 45]. The scientific method starts with the observation of how things are. Rational fluid therapy requires us to understand the contribution of suboptimal fluid therapy to surgical complications. Do complications caused by suboptimal fluid therapy (excluding negligent failure to treat or willful overdose) lead directly to surgical mortality? Ghaferi and colleagues at the Centre for Health Care Outcomes and Policy observe in various surgical patient populations that complication rates are broadly similar between hospitals with very low mortality rates and very high mortality rates [46]. From the information they gather, they move to the second step of the scientific method and propose a hypothesis. It is their hypothesis that higher surgical mortality rates across hospitals are largely explicable by an institutional failure to rescue patients who develop complications. The third step of the scientific method is to test that hypothesis in a reproducible controlled experiment, but there are clear ethical difficulties here. Fluid therapy researchers have to focus on complication rates rather than mortality, as they are far more common and are presumed, rightly or wrongly, to lead to mortality, as well as increasing the costs of achieving the desired final outcome. They have designed randomized controlled trials (RCTs) of protocol A versus protocol B but they are rarely reproducible. The fourth step, analysis of the data from the experiment, usually fails to deliver incontrovertible conclusions, and the underlying hypothesis is rarely questioned. The ultimate step will be to reproduce experiments that deliver confirmation of hypotheses.

A classification of post-surgical complications, first published in 1992, was critically re-evaluated, modified and retested to increase its accuracy and its acceptability in the surgical community. The new Clavien–Dindo Classification was prospectively validated in a cohort of 6336 patients who underwent elective general surgery [47] and has gone on to gain wide acceptance as a system for recording complications and their severity [48]. A recent clinical trial of a nutritional intervention in patients undergoing elective colorectal surgery with primary anastomosis at six clinical centres in the Netherlands and Denmark found the commonest adverse events to be postoperative ileus (20–30%), anastomotic leakage (circa 10%) and pneumonia (less than 10%) [49]. Fluid overload would be suspected as a possible contributor to such complications. Intraoperative Continuous Intestinal Loop Warming (ICLW) reduces the incidence and duration of post-surgical ileus [50].

Varadhan and Lobo made a very helpful contribution to definitions in their meta-analysis of nine randomized controlled trials of intravenous fluid therapy in major elective open abdominal surgery [51]. They defined restricted fluid therapy as less than 1.75 l of "maintenance fluid" per day. Liberal fluid therapy was defined as more than 2.75 l per day for "maintenance fluid" per day. As Twigley and Hillman had commented 25 years earlier, the "standard" maintenance fluid prescription is based on the needs of a physiologically unstressed adult and is typically 3 l of water and 150 mmol sodium per day, which falls within their definition of liberal. Finding no difference in the complication rate between liberal and restricted strategies, Varadhan and Lobo reclassified patients according to fluid balance; balanced being zero volume balance with little or no weight change. Patients exposed to imbalance appeared to experience a higher complication rate. Their hypothesis is supported by bio-impedance data confirming the expectation that fluid imbalance is associated with ascites or fluid collections during the postoperative period in patients undergoing hepato-pancreatico-biliary operations [52]. Zero-balance, or euvolemic goal-directed fluid therapy (GDFT), is increasingly seen as good perioperative practice [53].

Clinical Research

Doherty and Buggy reviewed the evidence on perioperative fluid therapy volumes up to 2012 [54]. There was very little modern research with which to work. In 2003, Brandstrup's Danish multicenter study randomized 172 patients undergoing colorectal surgery to restricted (zero-balance) or liberal (anesthetist's standard) fluid therapy [55]. There were fewer complications and no deaths in the restricted group, while the standard group included four deaths and more complications. Mackay had found no advantage for a restricted protocol in a trial that randomized 80 patients undergoing colorectal surgery [56]. In Denmark, Holte randomized 48 American Society of Anesthesiologists (ASA) grade 1–3 patients undergoing day case cholecystectomy to liberal (40 ml/kg) or restricted (15 ml/kg) perioperative fluid therapy. Those receiving liberal therapy had fewer postoperative problems and were more likely to achieve same-day discharge [57]. She then randomized 32 ASA 1–3

patients undergoing inpatient colonic surgery and found better postoperative arterial oxygenation with restrictive therapy [58]. In the same year, she published a study that randomized 48 ASA 1–3 patients undergoing knee prosthetic surgery and found early postoperative pulmonary function to be better with liberal fluid therapy [59]. Doherty and Buggy expressed their view that a "restrictive" intraoperative fluid regimen, avoiding hypovolemia but limiting infusion to the minimum necessary, is likely to reduce complications after complex surgery. A single-centre chart review of 1242 colorectal surgeries later confirmed that greater perioperative fluid volume was independently associated with prolonged duration of recovery across a spectrum of surgical risk profiles [60]. In the contrasting clinical context of relatively low-risk patients undergoing ambulatory surgery, Doherty and Buggy are convinced that high-volume crystalloid infusion (20–30 ml/kg) reduces postoperative nausea and vomiting, dizziness, and pain. Those who advocate liberal fluid for symptom amelioration associated with ambulatory surgery, which induces only mild physiological stress response, usually do not take into account the increased risk of deep vein thrombosis [61]. Twigley and Hillman had worked at Charing Cross Hospital in London where Professor Greenhalgh's team had conducted their thrombosis research, and so they shared the view that infusion of any intravenous fluid is of doubtful value for patients undergoing minor to moderate surgery who will be able to drink within 24 h, and may expose the patient to the risk of late thrombo-embolic complication. I was myself a junior anesthetist at Charing Cross Hospital at the time, and was taught to defer fluid therapy during minor to moderate surgery. If necessary, deferred fluid can be administered once the patient has recovered from anesthesia and is moving her legs.

Observation of a laparoscopic bariatric surgical practice over 1 year included 224 patients. Patients who received less than 1750 ml of intraoperative fluids experienced longer hospital length of stay when compared to patients who received more than 1750 ml. The best outcome was experienced by patients receiving liberal intraoperative infusion rates (more than 7 ml/kg/h), among whom only 15% had extended length of stay. Lower rates of intraoperative fluid administration were also associated with delayed wound healing [62].

Researchers in Plymouth, England, used a liberal perioperative fluid protocol (about 13 ml/kg/h) on 220 patients undergoing rectal resection or cystectomy, and randomized them to an intervention group who received additional modified fluid gelatine to achieve hemodynamic goals according to stroke volume variation. Endpoint was serious complications by Day 5, and they found no difference between the groups. They did, however, concede that the observed complication rate for patients in their study was relatively high [63]. In another study of cystectomy surgery, Wuethrich and colleagues found fewer complications, including death, in patients managed with a restrictive deferred hydration strategy, aided by a preemptive low-dose norepinephrine infusion [64]. Researchers in Melbourne, Australia, used a restricted perioperative fluid strategy for 100 patients undergoing colorectal surgery and randomized half their patients to additional fluid therapy guided by optimization of stroke volume index. They found no difference in postoperative complications [65].

The international multicenter randomized controlled trial called RELIEF (REstrictive versus LIbEral Fluid Therapy in Major Abdominal Surgery) succeeded in recruiting almost 3000 patients within 3 years, and was published in 2018 [66]. It is a matter of great regret that modern enhanced recovery principles were not consistently applied in the care of these patients, and that there was no Usual Care control group. Patients in the liberal fluid group received a perioperative median of 6 liters, and those in the restrictive fluid group received a median of 3.7 l. However, the resulting increase in body weight (along with fluid retention) was modest—just 1.6 kg in the liberal fluid group and 0.3 kg in the restrictive fluid group. Indeed, a quarter of the patients *for whom weight data were available* (my emphasis) suffered fluid deprivation with a weight loss of greater than 1 kg at 24 h after surgery. The headline conclusion was that the restrictive fluid protocol was not associated with a higher rate of disability-free survival than their liberal fluid regimen 1 year after surgery, but was associated with a higher rate of acute kidney injury.

By way of response, surgeons at the Mayo Clinic examined their own data set of more than 40,000 patients undergoing elective colorectal procedures within an enhanced recovery pathway [67]. In their hands the incidence of early acute kidney injury was much lower at 2.5% than either of the RELIEF protocols (8.6% and 5%), and long-term sequelae were exceptionally low. Of course, they may have been operating on a healthier patient population, but the finding that acute kidney injury patients received higher fluid volume on the day of surgery (3.8 ± 2.4 vs. 3.2 ± 2 L, $p = 0.01$) ran contrary to the RELIEF study message. The association between acute kidney injury and increased postoperative weight gain at the Mayo Clinic was even stronger at post operative day 2 (6 ± 4.9 vs. 3 ± 2.7 kg, $p = 0.007$), but could have been a consequence of the harm rather than its cause.

One reason for less fluid retention in this trial may be that many surgical procedures performed today are minimally invasive, which reduces the metabolic stress that leads to arginine vasopressinaemia. Another reason may be the hypotonic or balanced intravenous fluids that were administered in the current study, which were associated with a lower osmotic load than isotonic fluids.

Special Case Surgery?

In recent years there have been several observational and retrospective reports of perioperative fluid protocols to reduce specified complications of certain surgical procedures. Transsphenoidal pituitary surgery is often complicated by hyponatremia, but a retrospective review of 344 patients showed no evidence that fluid restriction or diuretic therapy was helpful [68]. Data from 65 neonates undergoing systemic-to-pulmonary artery shunt surgery showed no correlation between the time to negative fluid balance and the duration of mechanical ventilation or hospital length of stay [69]. In 365 male patients undergoing rectal cancer surgery, intraoperative fluid restriction did appear to reduce the risk of post-surgical urinary retention [70]. 40 patients undergoing lung resection were maintained on a

euvolaemic (volume balanced) perioperative fluid protocol with preserved global end diastolic volume and increased cardiac output but no increase in lung water volume. Three patients (7.5%) did, however, experience acute kidney injury [71]. In 1442 lung resection patients from another centre the incidence of acute kidney injury was around 5% but appeared to be unrelated to crystalloid therapy volume. Acute kidney injury occurred more often amongst patients given hydroxyethyl starch [72]. Data from 54 patients randomized patients undergoing pancreatic surgery with lower (5 ml/kg/h) or higher (10 ml/kg/h) fluid infusion rates showed no differences in indicators of recovery of gastrointestinal function [73]. Intraoperative fluid restriction in patients undergoing pancreatic surgery has not yet been shown to affect postoperative outcome [74]. Surgeons at Duke Medical Center, USA, use a fluid restricted protocol in kidney donor surgery in the belief that restricted use of intraoperative fluids prevents excessive third spacing and bowel edema, enhancing gut recovery without adversely impacting recipient graft function [75]. Intraoperative fluid restriction has also been used in 164 Living liver donor hepatectomy cases with the intention of achieving low central venous pressure with reduced blood loss while avoiding acute kidney injury [76]. Severe intra-operative declines in renal function have been observed shortly after liver transplantation. Elevation of renal oxygen consumption occurs but is not matched by a proportional increase in renal oxygen delivery [77]. In 147 patients undergoing brain surgery, goal-directed fluid restriction protocol was associated with a reduction in intensive care unit length of stay and costs, and a decrease in postoperative morbidity [78]. Amongst 169 patients who underwent cytoreductive hyperthermic intraperitoneal chemoperfusion at the University of Massachusetts Medical School, restrictive intraoperative fluid therapy was associated with lower post operative morbidity and reduced length of hospital stay [79].

Safely Implementing a Smaller Volume Approach to Perioperative Fluid Therapy

Fluid Balance Monitoring

With general acceptance that perioperative fluid deprivation (negative fluid balance) predisposes to renal injury it is surprising that unintentional fluid deprivation is not uncommon and compliance with fluid balance monitoring in practice remains inadequate [80–83]. Quality initiatives are indicated, especially if very restrictive policies are to be implemented.

Infuse Colloids?

The whole *raison d'aitre* of biophysical colloid osmotic pressure therapy is to achieve elevated central volume of extracellular fluid while keeping the tissue

volume low. There are many problems with this strategy, not least that it is far less effective than is widely anticipated. 2004 saw the publication of two landmark papers.

- In a large randomized clinical trial comparing albumin and saline for fluid resuscitation in a general intensive care patient population, it was observed that the volume of human serum albumin solution required to achieve resuscitation on the first day (mean 1.2 l) was only a little less than the effective volume of 0.9% sodium chloride (mean 1.6 l), and that albumin-treated patients received more red cell transfusions in the first 2 days [14].
- In a laboratory study it was shown that "colloid osmotic forces opposing filtration across nonfenestrated continuous capillaries are developed across the endothelial glycocalyx and that the oncotic pressure of interstitial fluid does not directly determine fluid balance across microvascular endothelium" [11].

In 2009, researchers in Amsterdam confirmed, by clinical experiments in both septic and nonseptic patients, that reducing colloid osmotic pressure of plasma does not predispose to pulmonary edema, and that colloid resuscitation does not reduce the risk [84]. In the hope that hydroxyethyl starch might succeed where albumin had failed, a large randomized controlled trial was published in 2012 and confirmed that the plasma substitute causes more harm than isotonic salt solution and has very little volume advantage in clinical resuscitation [15]. In 2013 it was shown that perioperative stroke volume optimization goal-directed fluid therapy is possible with crystalloid, and there is no evidence of a benefit in using hydroxyethyl starch. The authors declared that "the concept of the 1:3 replacement ratio in hypovolemic patients is obsolete" [85]. A 2016 Cochrane meta-analysis of colloids versus crystalloids in critically ill, trauma and surgical patients found 59 clinical trials involving nearly 17,000 patients showing no clinical advantage for the use of colloids. In trials recruiting patients with sepsis colloid use increased the risk of developing acute kidney injury requiring renal replacement therapy [86]. It is sometimes speculated that colloids do not harm patients undergoing uncomplicated surgery, but it is established that they confer no advantage over crystalloids. Trauma, surgery, and sepsis are all associated with systemic inflammatory response with increased capillary escape rate for albumin, and there is no reason to distinguish them for the purposes of rational fluid prescribing.

The Cochrane collaboration continues to advise against the use of colloids for volume resuscitation [87]. While some anesthetists still feel incapable of managing surgical patients without biophysical osmotic therapy, the volume kinetic fact is that the rate of elimination of crystalloid infusions is greatly retarded by general anaesthesia [88]. Crystalloids will do the job in the operating room.

The advantages that early physiologists predicted for intravenous biophysical colloid osmotic pressure therapy do not happen, and trials show more signal for harm than for benefit. A full appreciation of modern Starling physiology points to better ways to influence the intravascular—extravascular volume ratio.

Oliguria

A systematic review in 2016 examined the significance of peri-operative oliguria in randomized controlled trials. The incidence of oliguria tended to be greater with restrictive protocols, but there were too few data to achieve statistical significance. Oliguria occurs even in patients given liberal fluid volumes. Acute renal failure occurred equally in restrictive and liberal groups [89]. Enhanced recovery pathways are increasingly de-emphasising the traditional half a ml per kg rule. Acknowledging that obligatory urine volume is not proportional to body weight, I have personally suggested that oliguria in adult patients should be defined as less than 80 ml in any consecutive 4 h. In a recent study restrictive hydration with norepinephrine administration was as safe for renal function as liberal hydration intraoperatively [90]. Low-dose alpha −1 agonist infusion counteracts anesthesia-associated oliguria and may be a more effective approach than giving more fluid.

Thirst

There is an interesting hypothesis that the experience of thirst is a good indicator of need for additional intravenous fluid. A system that delivers intravenous fluid in response to subjective thirst has been designed, and can correct fluid deficits in healthy volunteers. The next step will be a feasibility study to assess this system in the perioperative setting [91].

Reduce Venous Capacitance

While euvolemic cardiovascularly fit patients should not need hemodynamic support under anesthesia that is not too deep, higher-risk patients are sometimes given a titrated dose of vasopressor to maintain vascular tone. See, for example, the protocol of Jacob *et al* [26]. In higher (hypertensive) doses the alpha-1 effect is predominantly precapillary vasoconstriction, while there is experimental evidence that propofol-induced hypotension is largely due to postcapillary venodilation and is more appropriately treated by restoring the mean systemic pressure and the venous excess volume. Robert Hahn has shown in a human clinical experiment that an infusion of phenylephrine 0.001 mcg/kg/h prevents anesthesia-induced hypotension by slowing distribution of infused crystalloid from the central to the peripheral fluid kinetic volume and so preserving the plasma volume [92]. Through the lens of RSE&GM, I prefer to think of the mechanism as reduction of J_v due to reduced capillary pressure. Low-dose phenylephrine infusion increases urinary excretion, counteracting anesthesia-induced oliguria, without slowing heart rate or raising blood pressure, and does not reduce the plasma volume as might occur at a higher dose. Another conceivable advantage is alpha-1-mediated increased lymphatic spontaneous contractility, which would aid return of interstitial fluid to the

bloodstream. Wuethrich and colleagues have demonstrated that what they call preemptive norepinephrine infusion at 2 mcg/kg/h can be used to limit fluid balance and to improve patient outcomes after cystectomy [64].

Sodium Dose

Physiology predicts there will be very little, if any, excretion of electrolyte-free water in many hospitalized patients, because arginine vasopressin opens aquaporin-2 channels of the renal collecting ducts making them permeable to water. The clinical importance of what we might call arginine vasopressinemia is too often ignored by modern fluid guideline writers. Many of the drugs given to adults in hospital either stimulate the further release of arginine vasopressin or increase the sensitivity of arginine vasopressin receptors. Disorders of volume and tonicity are therefore the most common serious problems associated with intravenous fluid therapy. An editorial comment warned that "there can be no justification for administering hypotonic fluids in the perioperative setting" [93]. Moritz warned anesthesiologists that their most stressed trauma and surgery patients are under the endocrine influence of arginine vasopressin and are very susceptible to symptomatic reductions in plasma sodium when fluid, even an isotonic solution, is infused. He recommends 0.9% sodium chloride in glucose 5% solution for postoperative fluid maintenance, and cautions that no hypotonic infusions should be given to patients whose plasma sodium is <138 mmol/l. In neurosurgical practices hypertonic salt solutions may have to be used to keep plasma sodium well above 140 mmol/l [94]. Surgeons at Thomas Jefferson designed a study to determine whether 3% hypertonic saline could reduce the volume of fluid required to sustain tissue perfusion in the perioperative period and improve outcomes for pancreaticoduodenectomy patients. Two hundred sixty-four patients completed the study, which confirmed that perioperative hypertonic saline prescription achieves smaller net fluid balance and reduces complications [95]. Moritz and I have criticized UK guidance, which unfortunately advocates fifth normal saline in glucose for postoperative fluid therapy [96, 97]. Vulnerable patient groups are:

- Children and young adults who normally have a higher proportion of intracellular to extracellular fluid volume within the cranial cavity
- Patients with deficient blood–brain barrier including meningitis, encephalitis, trauma, tumor
- Older adults and patients with neuromuscular disorders leading to reduced muscle mass, which is a major extracellular fluid reservoir
- Premenopausal adults (estrogen)
- Trauma or surgery (arginine vasopressin)
- Concurrent drugs including morphine, nonsteroidal anti-inflammatory agents, anticonvulsants (arginine vasopressin)
- Endocrine abnormalities including hypothyroidism, adrenal insufficiency, syndrome of inappropriate antidiuretic hormone (ADH) secretion

We must dispel any notion that any one intravenous fluid is somehow superior to another, or that there can ever be a single universal resuscitation or maintenance fluid. The earliest isotonic salt solution was described by the Dutch physiologist Hartog Hamburger. Armed with Hamburger solution (0.9% sodium chloride), 1.26% sodium bicarbonate and 5% glucose solutions, plus potassium supplements as needed, the intelligent prescriber can match the fluid and electrolyte needs of almost any individual patient under his care. If it becomes necessary to infuse more than 2 l (30 ml/kg) of isotonic salt solution in a day, chloride/ bicarbonate balance and plasma acid/ base status may become significant considerations. We do not know whether hyperchloremia is more to be feared than hypochloremia, and it is quite possible that abnormal serum chloride is a symptom of the underlying disease rather a complication of fluid therapy. A Cochrane collaboration found that the administration of isotonic sodium chloride (unbuffered) or buffered fluids to adult patients during surgery are equally safe and effective [98]. The use of buffered fluids is associated with less hyperchloremia but the clinical significance of chloremia is not known. Nonetheless, the intelligent prescriber can either use both isotonic sodium chloride and isotonic sodium bicarbonate in appropriate proportions, or prefer a so-called balanced salt solution. For some reason British and Antipodean anesthetists honor the American pediatrician Hartmann and often use his solution, while Americans and Europeans honor the English physiologist Ringer and use his lactated solution. Hartmann's and Ringers lactate are essentially the same. They are hypotonic rather than isotonic solutions and it would be dangerous to use them in the resuscitation of vasopressinemic patients who are susceptible to harm from hyponatremic encephalopathy. Consider the following calculated example of how harm can ensue. The osmolalities of plasma, 0.9% sodium chloride and Hartmann's solution are about 288, 286, and 256 mosmol/kg, respectively. We therefore expect infusion of Hartmann's solution to reduce plasma osmolality in a dose-dependent fashion in patients who cannot excrete a free water load. Consider what happens with just a 3% reduction in plasma/extracellular fluid osmolality from 288 to 280 mosmol/kg; there will be a 3% (40 ml) increase in intracellular brain volume, which must cause a 40 ml (30%) decrease in intracranial blood and cerebrospinal fluid volume. In a patient with critically compromised intracranial compliance, such a change can be fatal. Another consideration is that the infused lactate will make it impossible to use plasma lactate measurements as an indicator of tissue perfusion [99]. There are a number of isotonic balanced salt solutions that include anions other than lactate, and they could be a rational choice for your practice.

The restrictive fluid therapy protocol used in the University of Melbourne study is a reasonable template for patients undergoing major abdominal surgery. Carbohydrate drinks are supplied up to 2 h preoperatively. Intravenous fluid preload is not recommended, but a small postinduction bolus of up to 5 ml/ kg could be administered if hypotension is thought to be due to hypovolemia. Intraoperative balanced isotonic maintenance fluid rate was 300–400 ml/h (5 ml/kg/h), reduced after surgery to 40 ml/h (0.5 ml/kg/h for larger patients). Urine output criterion for postoperative oliguria is 120 ml per 4 h. Additional non-sanguinous fluid could be prescribed to replace blood loss, for which 2 ml crystalloid per milliliter of blood

should suffice in non-major hemorrhage, or to treat hypotension that did not respond to a vasopressor. In the United states Glucose 5% sodium chloride 0.9% is often used for maintenance infusion in acutely ill and major surgical patients, but for safety reasons this solution is very rarely used in adult practice in the United Kingdom [100]. In the United Kingdom, Enhanced Recovery After Surgery (ERAS) programs are widely adopted and advocate zero-balance fluid goals for uncomplicated surgery. Postoperative fluid therapy is to be kept to a minimum and oral intake encouraged. Postoperative oliguria (<0.5 ml/kg/h) is accepted if there is no other cause [53]. It is reported that uptake of ERAS in the United States has been slow, perhaps for fear of expense. Stone et al. suggest that financial savings are in fact attainable [101].

I was a contributing member of the recent Association of Anaesthetists of Great Britain and Ireland (AAGBI) report on perioperative care for diabetic patients. By consensus we suggested half-normal saline in glucose for routine postoperative maintenance in this patient subgroup receiving insulin therapy [102]. Where it is available, normal saline in glucose may be preferable. Hartmann's solution increases glycemia and is probably best avoided in diabetics.

Protect Lymphatic Pump Efficiency

There is a common misunderstanding that lymph is a passive overflow drainage system, when in fact it is part of a vital extracellular fluid circulation and is pumped by several mechanisms that can be optimized. Lymphatic smooth muscle responds much as cardiac muscle does to volume and neurohumoral factors. The rate of contractions and their strength are enhanced by alpha adrenergic agonists (lymphogogues) and inhibited by many inflammatory mediators, anaesthetic techniques and opioids. Intrathoracic pressure cycling moves lymph towards the central veins because lymphangions contain semilunar valves. Somatic muscle activity motivates lymph (and venous blood) flow.

Monitoring for Euvolemic Goal-directed Therapy

It is presumed that early detection of reduced stroke volume enables early correction and avoidance of inadequate tissue perfusion, which must be harmful. We can accept the premise that increasing ventricular responsiveness to cyclical changes in preload induced by mechanical positive-pressure ventilation precedes reduced stroke volume state, It has been found that, in experienced/expert hands, dynamic parameters such as arterial pulse pressure variation and stroke volume variation are reasonably accurate predictors of fluid responsiveness. There are, however, three important exceptions: (1) when tidal volumes are low or the patient is breathing spontaneously, (2) when the chest is open, and (3) during sustained cardiac arrhythmia. The utility of this strategy is to achieve zero-balance fluid management while avoiding hypovolemic circulatory compromise. Unfortunately, in the hands of

practicing anesthetists, an observational study of the randomized controlled trial OPTIMISE found that the predictive accuracy of stroke volume variation and pulse pressure variation for fluid responsiveness was not adequate for routine use during or after major gastrointestinal surgery. The data confirmed the established view that these variables should not be used for predicting fluid responsiveness in spontaneously breathing patients [103].

Brandstrup randomized 150 patients undergoing colorectal surgery to a zero-balance protocol or an optimal stroke volume protocol and found no difference in outcome [104]. Her fluid management involved hydroxyethyl starch in both treatment limbs. A Cochrane systematic review published in 2013 identified 31 studies involving 5292 patients. It highlighted the paucity of recent data concerning goal-directed therapy; Sandham's trial published in the *New England Journal of Medicine* a decade earlier, using pulmonary artery catheter monitoring, dominated the data set. The reviewers found that perioperative cardiac output monitoring did not reduce perioperative mortality, but might reduce the number of nonfatal renal and pulmonary complications and poor wound healing. and reduce the overall length of hospital stay by about 1 day. Rates of cardiac arrhythmia, myocardial infarction, congestive cardiac failure, venous thrombosis, and other types of infections were not reduced. They opined that the evidence did not support widespread use of perioperative cardiac output monitoring [105]. Later trials have supported their conclusion. Unsurprisingly, arterial pulse contour analysis did not improve outcomes for elderly spontaneously breathing patients under spinal anesthesia [106]. OPTIMISE enrolled 734 high-risk patients undergoing major gastrointestinal surgery and could not demonstrate an advantage for hyperdynamic therapy [107]. By the sophistry of adding their data to a meta-analysis, they were able to claim a statistically significant reduction in the complication rate. The OPTIMISE II trial is hoping to complete recruitment of 2500 patients by the end of 2019 (https://optimiseii.org/about}. On the current evidence, it is my view that stroke volume monitors that can be used pre- and postsurgery can be a valuable part of the expert anesthetist's intraoperative armamentarium to attain and maintain euvolemia, to be used on his/her clinical judgment. Rigid protocols that are allowed to override informed clinical judgment may be dangerous.

Monitoring for Hypervolemic/Hyperdynamic Goal-directed Fluid Therapy

Since the pioneering work of William Shoemaker in California, it has been hoped that supranormal stroke volume achieves supranormal oxygen delivery, which aids healing and reduces complications of surgery [108, 109]. The premise in this strategy is the same as for euvolemic GDFT, but the utility is to achieve a hyperdynamic state with least harm from edema. In Intensive Care practice, hyperdynamic therapy guided by cardiac output monitoring has been found to be ineffective at improving patient outcomes in three major studies [110–112]. A more recent study of 187 patients undergoing major surgery confirmed that patients achieving higher oxygen

delivery experience fewer complications, but that a protocol specifically targeting higher oxygen delivery does not improve surgical outcome [113]. In my view, this strategy is physiologically unsound as well as demonstrably ineffective and should no longer be pursued.

Avoid Fluid Boluses

One must exercise great caution in extrapolating fluid kinetics of healthy volunteers to patients. Nonetheless, Hahn's demonstration by volume kinetics that edema is a normal consequence of plasma volume expansion in healthy volunteers when crystalloid fluid is given rapidly, but the tendency for edema formation is small when the fluid is given slowly, is compelling [24]. While Hahn reasons that this is largely due to visco-elastic properties of the interstitial matrix, I feel that transendothelial hyperfiltration (excessive J_v) during transient peaks of capillary pressure is equally plausible. In an intra-operative patient study, neither colloid nor crystalloid boluses increased oxygen delivery, and only crystalloid boluses increase the glomerular filtration rate. Renal oxygen consumption rose along with the increase in glomerular filtration but was not matched by a proportionate increase in renal oxygen delivery, raising concern about adequate renal oxygenation [114]. Such evidence provides physiological reasons why bolus therapy was observed to be harmful in the Fluid Expansion As Supportive Therapy (FEAST) trial [16]. It is my view that research is urgently needed on the role of bolus fluid therapy. Until more evidence is available, clinicians should use smaller boluses at lower infusion rates, repeated as needed, to achieve the desired central fluid volume expansion.

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The Perioperative Use of Albumin

10

Ehab Farag and Zeyd Y. Ebrahim

Abstract

Human serum albumin (HSA) is the predominant product of hepatic protein synthesis and one of the more abundant plasma proteins. HSA is a monomeric multidomain macromolecule, representing the main determinant of plasma oncotic pressure and the main modulator of fluid distribution between body compartments. HSA displays an essential role in maintaining the integrity of the vascular barrier. HSA is the most important antioxidant capacity of human plasma, in addition to its ability to protect the body from the harmful effects of heavy metals such as iron and copper and reduce their ability to produce reactive oxygen radicals. HSA is the main depot for nitric oxide (NO) transport in the blood. HSA represents the main carrier for fatty acids, affects pharmacokinetics of many drugs, and provides the metabolic modification of some drugs and displays pseudo-enzymatic properties. HSA has been widely used successfully for more than 50 years in many settings of perioperative medicine including hypovolemia, shock, burns, surgical blood loss, sepsis, and acute respiratory distress syndrome (ARDS). Recently, the use of HSA has shown a promising neuroprotective effect in patients with subarachnoid hemorrhage. The most recent evidence-based functions and uses of HSA in the perioperative period are reviewed in this chapter.

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Key Points

1. Human serum albumin is the most abundant protein in the body.
2. Human serum albumin represents the most important antioxidant agent in the human plasma.
3. Human serum albumin is the main depot for nitric oxide transport in the blood.
4. Human serum albumin plays a very important role in maintaining the integrity of vascular barrier and endothelial glycocalyx.
5. Human serum albumin is successfully used in many settings of perioperative medicine.

Introduction

Human serum albumin (HSA) is the most abundant protein in the human plasma (40–50 g/L). HSA has many functions; it is the main regulator of the vascular barrier, antioxidant in the plasma, and transporter of nitric oxide (NO) and fatty acids and drugs.

HSA infusions have been used successfully for more than 50 years since World War II in many perioperative settings such as shock, volume expansion, burns, cardiopulmonary bypass, acute liver failure, sepsis, and many more. Recently, its use has been questioned following a widely publicized meta-analysis in 1998 that reported increased mortality in patients who received albumin solutions; the role of albumin administration in critically ill patients became highly controversial. However, the results of this meta-analysis have been challenged by several meta-analyses, randomized controlled trials that not only proved the safety of HSA but its benefit especially in patients with sepsis, liver failure, hypoalbuminemia, and burns [1–4]. The most recent evidence-based functions and uses of HSA in the perioperative settings are reviewed in this chapter.

Albumin Gene and Structure

Human serum albumin (HSA) is a non-glycosylated, negatively charged plasma protein. HSA is a single polypeptide chain of 585 amino acids and has a molecular mass of 66.5 kDa. HSA consists of α(alpha)-helix but no β(beta)-sheet, and it consists of three homologous domains (I–III) that assemble to form a heart-shaped molecule. Each domain is composed of two subdomains (A & B) with distinct helical folding patterns connected by flexible loops. The center of the molecule is made up of hydrophobic radicals, which are binding sites for many ligands, while the outer part of the molecule is composed of hydrophilic ligands (Fig. 10.1) [6].

HSA is a member of the albumin superfamily, which also includes α(alpha)-fetoprotein, vitamin D-binding protein, and afamin (α[alpha]albumin). HSA synthesis is governed by a single copy gene lying on the long arm of chromosome 4, near the centromere for the long arm, at position 4q11-13. The mRNA for HSA

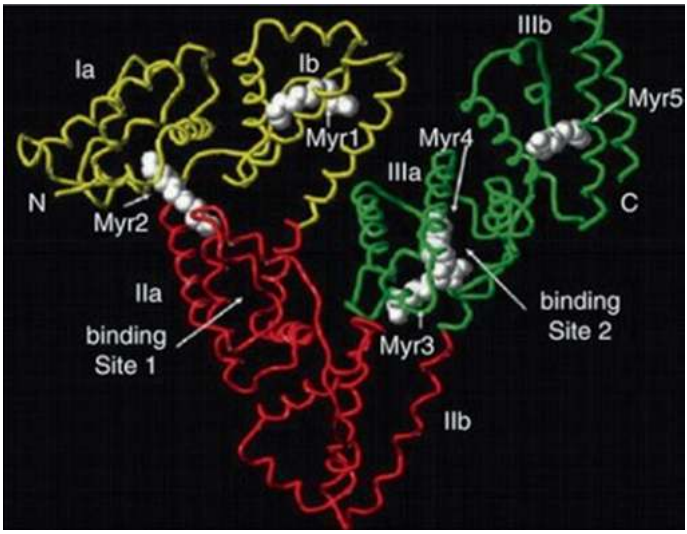

Fig. 10.1 X-ray structure of human serum albumin (Reprinted with permission from Kratz [5]. Proceedings of the Tenth European Symposium on Controlled Drug Delivery)

encodes a precursor protein (preproalbumin) of 609 amino acid residues. Cleavage of the single peptide of 18 residues and the propeptide (proalbumin) of 6 residues yields the mature protein of 585 residues [7].

Albumin and Its Role in Endothelial Barrier

HSA plays an integral role in maintaining the integrity of the vascular barrier. HSA enhances the integrity by electrostatic binding to the negatively charged heparin sulfate side chains of core glycoproteins such as syndecan-1 and glypican-1 of the endothelial glycocalyx via its positively charged arginine residues and enhances the availability of sphingosine-1-phosphate (S1P) produced by red blood cells (RBCs). Extracellular sphingosine is taken up and phosphorylated by RBCs sphingosine kinases (SK) into S1P that is stored in the cell membrane of RBC. S1P is extracted from the RBC membrane by Apo lipoprotein M (ApoM) of high-density lipoprotein (HDL) (Apo lipoprotein M is the principal partner of S1P in HDL) and HSA, and this ensures a constant supply of receptor-available S1P for cellular signaling purposes. In contrast to the bond formed between S1P and HDL, HSA facilitates the solubility of S1P in the aqueous solution but not in physical bond to HSA. This unbound S1P is the active form of S1P. It is worth mentioning that one S1P molecule is extracted by 500 serum albumin molecules, indicating that HSA does not physically bind S1P [8–10]. S1P activates the G protein-coupled S1P1 receptor, which rapidly activates the Rho family small GTPase Rac1 in the endothelial cells, leading to peripheral localization of cytoskeletal effectors (cortactin and nonmuscle

myosin light chain kinase). This localization promotes adherents' junction (including vascular endothelial-cadherin and associated catenins) and tight junction (occluding, zonula occludens proteins and claudins) formation. Therefore, S1P improves the vascular barrier and stabilizes the endothelial glycocalyx. S1P has been found to reduce matrix metalloproteinase activation, thereby attenuating the loss of endothelial cell surface glycocalyx components. Both actions appear to involve signaling via the S1P receptor [11].

Albumin as a Major Antioxidant

Oxidative stress is defined as a disturbance in pro-oxidant and antioxidant balance leading to damage of lipids, proteins, and nucleic acids. According to Halliwell and Whiteman, an antioxidant is a substance that, when present at low concentrations compared with those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate [12]. Human serum albumin represents a major antioxidant agent in human plasma. The antioxidant activity of HAS results from the redox properties of the Cysteine 34 (Cys 34) and from metal-binding abilities. Among the metal ligands, copper (Cu) and iron (Fe) are very important, as they are able to generate reactive oxygen species (ROS) after a reaction with oxygen. Free Cu (I) and Fe (II) ions can react with H_2O_2 leading to the formation of the deleterious hydroxyl radical via the Fenton reaction. Cu(I) and Fe(II) binding to HSA promotes their oxidation to Cu(II) and Fe (III), thereby limiting their ability to participate in Fenton reaction. Copper ions bind to HSA with high affinity at the N-terminal tripeptide Asp-Ala-His. The first four amino acids of the N-terminus of HSA, Asp-Ala-His-Lys (DAHK), form a tight binding site for Cu(II) ions. DAHK/Cu has a superoxide dismutase activity, which thereby reduces the ROS generation. By trapping Cu(II), HSA prevents low-density lipoprotein (LDL) lipid peroxidation. Moreover, HSA and the tetrapeptide (DAHK) were shown to prevent neuronal death in murine cell cultures exposed to oxidative stress generated by H_2O_2/Cu(I)/ascorbic acid reagent [13]. Therefore, the binding of Cu ions with albumin is considered one of the most important antioxidant functions of albumin as Cu can react with H_2O_2 to hydroxyl radicals 60 times faster than Fe.

HSA is important for heme-Fe scavenging, providing protection against free heme-Fe oxidative damage. During the first seconds after heme-Fe appearance in plasma, more than 80% of this powerful oxidizer binds to HDL and LDL, and only the remaining 20% binds to HSA and hemopexin (HPX). Then, HSA and HPX remove most of the heme-Fe from HDL and LDL. Afterward, heme-Fe transits from HSA to HPX, which releases it into hepatic parenchymal cells after internalization of the HPX-heme-Fe complex by CD91 receptor-mediated endocytosis. It should be mentioned that kinetics of heme-Fe transfer from HDL and LDL to HSA and HPX is faster than the heme-Fe-induced lipoprotein oxidation [14, 15].

Albumin-bound bilirubin confers an antioxidant effect by inhibiting lipid peroxidation. Bilirubin bound to albumin was shown to protect α(alpha)-tocopherol from damage mediated by peroxyl radicals and to prolong the survival of human

ventricular myocytes against in situ–generated oxidative stress [16, 17]. Cholesterol undergoes oxidation in vitro and in vivo, forming biologically active derivatives known as oxysterols. Oxysterols bind to albumin with high affinity. Oxysterols carried by albumin are less rapidly released to cells than cholesterol. By this, albumin could limit detrimental effects of oxysterols on cells. Furthermore, binding homocysteine by HSA protects from atherosclerosis as elevated plasma homocysteine is a well-known risk factor for atherosclerosis (Figs. 10.2 and 10.3) [20].

Physiologically, HAS exists predominately in a reduced form (i.e., with free thiol, HSA-SH) and is known as mercapto-albumin. However, a small but significant

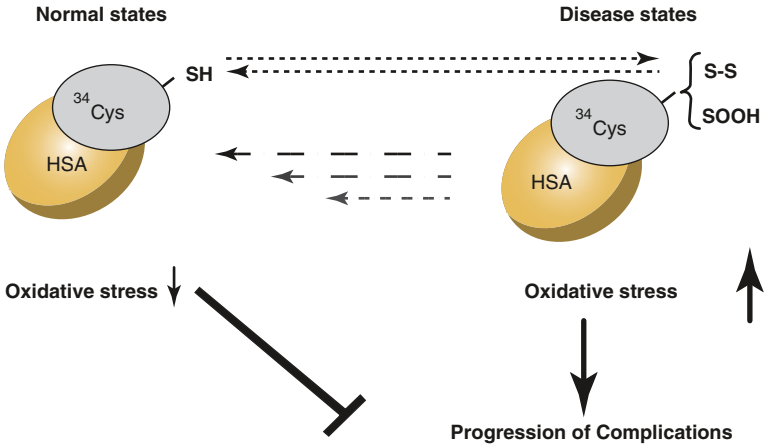

Fig. 10.2 Proposed mechanism for the contribution of Cys34 to the maintenance of homeostasis in blood. The treatments where the levels of Cys34 oxidation are minimized at low levels in several diseases may be beneficial for preventing the onset and progression of serious complications, which affects the prognosis for survival (Reprinted with permission from Anraku et al. [18])

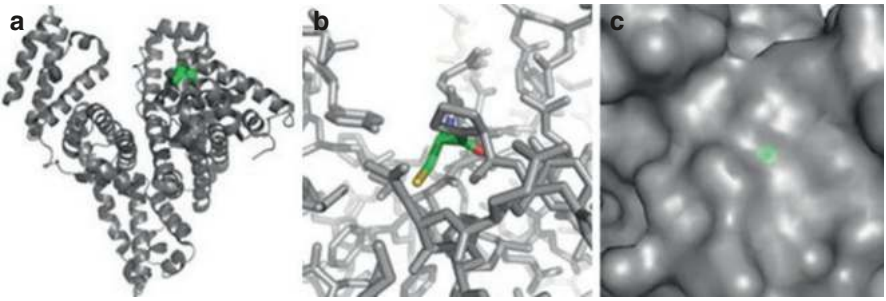

Fig. 10.3 Three-dimensional structure of human serum albumin, local environment, and surface exposure of Cys34. (**a**) Cys34 is shown in *green*. (**b**) Thiol microenvironment: C, *green*; O, *red*; N, *blue*; S, *yellow*. (**c**) Surface exposure of Cys34. Atomic coordinates were downloaded from Protein Data Bank, Accession Code 4EMX. The figures were prepared using PyMOL v0.99 (www.pymol.org) (Reprinted with permission from Turell et al. [19])

proportion of albumin pool exists as mixed disulfides (HSA-S-S-R); where R represents low-molecular-weight, thiol-containing substances in plasma—chiefly cysteine and glutathione [21]. Mixed disulfide formation increases as part of the aging process and during disease processes characterized by oxidative stress that enhances endothelial cell damage through oxidative stress and increase in apoptosis levels. Cysteine 34 (Cys 34) represents the largest fraction of free thiol in human plasma, HAS being the most abundant protein in plasma. Cys34 is located at the surface of HAS, close to Aspartate 38 (Asp38), Histidine 39 (His39), and Tyrosine 84 (Tyr 84). These three residues affect the ionization state of Cys34, thus modulating its reactivity [14]. In healthy adults, about 70–80% of the Cys34 in albumin contains a free sulfhydryl group, whereas about 25–30% of the HSA molecules have Cys34 forming a mixed disulfide with either cysteine or homocysteine or glutathione, thus affecting the Cys34 redox potential. Oxidation of Cys34 leads to the formation of sulfenic acid (RSOH), which is further oxidized to sulfinic (RSO_2 H) or sulfonic acid form (RSO_3 H). Sulfenic acid constitutes a central intermediate in both the reversible and irreversible redox modulation by reactive species. Reactive nitrogen species (RNS) constitute nitrogen-centered species analogous to ROS. RNS such as nitric acid (NO) contribute to various biological processes. HSA acts as a NO depot and a NO transducer. Moreover, 82% of NO in blood (~7 μM) is transported as an S-nitrosothiol bound at the HSA residue Cys34. S-nitrosylated HSA may represent a circulating endogenous reservoir of NO and may act as an NO donor. S-nitrosylated HSA acts primarily as a vasodilator in vivo and represents a stable reservoir of NO that can be released when the concentrations of low-molecular-weight thiols are elevated [22]. S-nitrosylated HSA has been shown to reduce either ischemia or reperfusion injury in pig and rabbit hearts after unprotected warm ischemia through long-lasting release of NO [14]. Other RNS, such as peroxynitrite (ONOO−), constitute powerful oxidants and nitrating species [23]. The -SH group of albumin represents an important antioxidant against peroxynitrite as the thiol group was oxidized to a sulfenic acid (HSA-SOH). Subsequently, HSA-SOH can be converted to a disulfide and then back to mercapto-albumin (HSA-SH). HSA administration favorably influences plasma thiol-dependent antioxidant status, as well as levels of protein oxidative damage in patients with sepsis and acute respiratory distress syndrome (ARDS) [24, 25]. Moreover, HSA is able to scavenge strongly oxidant compounds such as hypochlorous acid (HOCI) and hypothiocyanous acid. Cys34 is oxidized preferentially by hypochlorous and hypothiocyanous acid with the corresponding sulfenyl derivative. HSA is able to scavenge HOCI, preventing alteration of its preferential biological target $\alpha(\text{alpha})_1$-antiprotease [26]. Interestingly, West Nile virus is neutralized by hypochlorous acid-modified HSA that binds to domain III of the viral envelope protein E [27].

During its long life (~3 weeks), an HSA molecule makes 15,000 passes through the circulation, incurring some damages that affect its ligand-binding and antioxidant properties. Diabetes mellitus is one of the main pathological conditions that impairs the antioxidant functions of albumin. In this disease, albumin undergoes

increased glycation. The level of glycated HSA in normal humans is about 10%, and increased to 20–30% in hyperglycemic patients. Glycation corresponds to the non-enzymatic attachment of glucose molecule to a free amine residue. HSA glycation is associated with oxidation of His and Trp residues, main chain fragmentation, and loss of both secondary and tertiary structure. Both the use of diclofenac, a nonsteroidal anti-inflammatory drug (NSAID) and aspirin reduces the levels of advanced glycation [28]. The glycation of HSA impairs its antioxidant activity and its copper-binding ability. Glycation of HSA induced a marked loss of its antioxidant activity to copper-mediated oxidation of LDL, probably by the generation of superoxide. Moreover, the Fe(III)-binding antioxidant capacity of HSA is markedly reduced in diabetic patients. Finally, the HSA transport of tryptophan (Trp), which is the largest and essential amino acid, is reduced after its glycation. HSA glycation alters the binding of endogenous and exogenous ligands; in particular, glycation of Lys 199 enhances warfarin binding, but decreases bilirubin affinity [14].

Several receptors for advanced glycation end products initiate intracellular signaling and enhance ROS formation in the cells through recognition and binding of glycated (macro) molecules including HSA. Moreover, hypochlorous acid-mediated carbonylation of Lys residues of glycated HSA represents a major antigenic advanced glycation end product in hyperglycemia and in inflammation [29]. Glycated albumin was shown to impair vascular endothelial NO synthase activity in vivo in aortas of rabbits [30]. Glycated HSA displays a toxic effect on microglial cells associated with impairments in cellular proteolytic systems, possibly reflecting the role of advanced glycation end products in neurodegenation.

HSA may protect other proteins including hemoglobin, insulin, and immunoglobin from glycation in the early stages of diabetes due to its long half-life and its high concentrations compared to other proteins [31]. The irreversible damages associated with diabetes such as retinopathy, nephropathy, neuropathy, and coronary artery disease could be attributed to reduced antioxidant properties of glycated HSA.

Alterations in antioxidant properties of HSA were very recently identified in vivo in patients with obstructive sleep apnea syndrome. This reflects the impaired antioxidant HSA activity, which is associated with the enhanced glycation level of HSA in patients with obstructive sleep apnea syndrome. That might have increased the perioperative risks in those patients [32].

Anticoagulant Effect

HSA has anticoagulant and antithrombotic functions. These functions may in part be mediated by the HSA capacity to bind NO forming S-nitrosothiols, thereby inhibiting the rapid inactivation of NO and allowing prolongation of its anti-aggregatory effects on platelets [33]. Therefore, the use of HSA might be very beneficial in cases with hypercoagulable conditions such as during the perioperative period.

Enzymatic Properties of HSA

The interaction between HSA and another molecule results in enzymatic activity. This property of HSA is called an enzyme-like or a pseudo-enzymatic activity. The esterase activity involving lysine (Lys) 199 is able to split acetylsalicylic acid (aspirin) into salicylic acid, which is released and the acetyl group is transferred to especially Lys 199. Therefore, aspirin but no other salicylates induce the aspirin resistance syndrome, as the acetylation of albumin molecule can be allergic. Asthma, rhinitis, and nasal polyps characterize aspirin resistance syndrome. Moreover, Lys 199 and penicillins can covalently bind via an aminolysis, generating a penicilloyl-containing peptide. The covalent labeling of Lys 199 can have clinical consequences. The penicilloyl-HSA complex has no antibacterial activity; however, it represents the major antigenic determinant of penicillin allergy. HSA acts as a phosphotriesterase activity, which thereby inactivates organophosphorus compounds. HSA can catalyze RNA phosphodiester bond cleavage; therefore, it participates in the degradation of endogenous extracellular RNA and of circulating pathogenic nucleic acids. HSA possesses enolase activity toward dihydrotestosterone, converting it from the 3-keto to the 3-enol form. In addition, HSA facilitates the isomerization and the stereoselective hydrolysis of glucuronide conjugates and the removal of glucuronide conjugates, thereby reducing their plasma levels by reversible and/or irreversible binding. Finally, HSA seems to have a significant role in both the biosynthesis and the elimination the prostaglandins. HSA has no enzymatic effects on leukotrienes or thromboxanes. However, it binds and thereby stabilizes thromboxane A_2. Binding could play a major role for the inactivation of these potent compounds, diminishing the biological activities of substances that may be harmful for the body if present in too large amounts [7, 14].

Hypoalbuminemia

Hypoalbuminemia is generally defined as serum albumin concentration ≤30 g/L and is usually very common in critically ill patients. The albuminemia could result from increased loss of HSA into the gastrointestinal tract, increased capillary permeability leading to redistribution from the intravascular to the interstitial space, and reduced hepatic synthesis of HSA caused by cytokines and stress of critical illness.

Hypoalbuminemia is considered an independent risk factor for worse outcomes in critically ill patients. HSA levels <20 g/L were associated with higher mortality risk in burn patients with 84% sensitivity and 83% specificity [34]. In surgical septic patients, every 1 g/L decrease in albumin below 23 g/L was associated with a 19.4% increase in hospital mortality and 28.7% increase in the incidence of multiple organ failure [35]. Moreover, in a meta-analysis of 90 cohort studies that evaluated hypoalbuminemia as a prognostic biomarker in acutely ill patients, each 10 g/L in serum albumin was associated with a 137% increase in morbidity, and a 71% increase in length of hospital stay [36]. Preoperative low serum albumin (<4.0 g/dL) was shown

to be an independent risk factor for acute kidney injury (AKI) following off-pump coronary artery bypass surgery (OPCAB). AKI was associated with prolonged stay in the intensive care unit (ICU) and hospital and a high mortality rate [37].

Human Serum Albumin Metabolism

HSA circulates from the blood across the capillary wall into the interstitial compartments, including cerebrospinal fluid, and returns to the blood through the lymphatic system with a circulation half-life of approximately 16 h. The movement of HSA across the capillary wall is defined as the transcapillary escape rate (5% per hour), which indicates the percentage of intravascular HSA leaving the intravascular compartment per hour [14]. In its long half-life of ~2–3 weeks, one HSA molecule could make about 15,000 passes through the circulation. HSA is mainly synthesized in the liver. In healthy young adults, about 12–25 g of HSA per day is synthesized in polysomes bound to endoplasmic reticulum of hepatocytes. HSA is not stored hepatically and there is therefore no reserve for release on demand [33]. Under physiological circumstances, only 20–30% of hepatocytes produce HSA and its synthesis can be increased up to 200–300% on demand. HSA synthesis is regulated by colloid osmotic pressure and the osmolality of the interstitial liquid around the hepatocytes. Insulin plays an important role in stimulating HSA synthesis; therefore, diabetic patients could suffer hypoalbuminemia. Estrogens do not affect HSA transcription, but act by modifying the stability of the HSA mRNA. HSA synthesis can be enhanced by corticosteroids, insulin, and amino acids administration. HSA synthesis can be rate-limited by amino acid deficiencies, but these are rarely seen clinically, except in states of extreme starvation and malnutrition [33]. In acute-phase reactions, such as in trauma and the perioperative period, the synthesis of HSA is depressed by hepatic cytokines such as interleukin-6 and tumor necrosis factor-α(alpha).

Immunoglobulin G (IgG) and albumin, despite their disparate forms and functions, have long been known to share two unique characteristics, namely, their lengthy life spans and inverse relationship between their serum concentrations and half-lives. The long half-lives are attributed to the efficient receptor-mediated recycling pathway involving the neonatal Fc receptor (FcRn). FcRn is a heterodimer of a nonclassical major histocompatibility class I (MHC I) α(alpha)-chain and $\beta(\text{beta})_2$ microglobulin ($\beta[\text{beta}]_2$m) that binds the two abundant serum proteins IgG and albumin in the body. FcRn binds both IgG and albumin simultaneously on the opposite sides of the receptor, where the net transport can be basolateral to apical, apical to basolateral, or apical to apical (endothelial cells). FcRn interacts with IgG and albumin in a strictly pH-dependent manner; therefore, it binds them at acidic pH and not at physiological pH. Pinocytosed IgG and albumin bound by the receptor within acidified endosomes are transported back to the cell surface where physiological pH of the blood triggers release of the ligands into the blood circulation. The intracellular nonbound fractions are targeted for lysosomal degradation. FcRn is also largely responsible for transporting the IgG across the placenta whereby the IgG

concentration in newborns at term normally exceeds that of the mother. Animals deficient in FcRn catabolize IgG and albumin more rapidly than normal animals and manifest low plasma concentrations of both molecules. Familial hypercatabolic hyoproteinemia, where deficiency of FcRn is due to mutation in $\beta(\text{beta})_{2m}$ results in hypercatabolism and low plasma concentrations of both albumin and IgG. However, patients with myotonic dystrophy (DM) exhibit plasma deficiency only in IgG but not albumin caused by reduced affinity of FcRn to IgG [38–40].

The catabolism of HSA takes place in several organs at a rate of about 14 g/day in a 70 kg healthy adult, or 4% of whole body protein turnover. The rate of HAS catabolism is increased by protein and caloric deprivation as HSA is used as a source of energy. The mechanism of HSA breakdown involves protein uptake into endocytotic vesicles, which fuse with lysosomes of endothelial cells.

Circulating HSA is also lost into the intestinal tract (about 1 g each day), where digestion releases amino acids and peptides that are reabsorbed. There is minimal urinary loss of HSA in healthy subjects. It is worth mentioning that of the 70 kg of HSA that passes through the kidneys each day, only a few milligrams are secreted from kidney tubules [14].

The Use of Albumin in Perioperative Settings

The Use of Albumin in Sepsis

The use of human albumin in critically ill and septic patients has been through much controversy in the last two decades. In 1998, a Cochrane meta-analysis for albumin administration in critically ill patients was published in the *British Medical Journal* [41]. The average sample size of the selected 32 studies in this meta-analysis was just 46 patients. The results of this meta-analysis showed increased mortality of almost 70% in patients given albumin. The results of this Cochrane report changed the practice rapidly around the world with dramatic reduction in albumin use especially in Europe. The validity of this meta-analysis has been disputed for several methodological reasons, such as omission of relevant trials, small trials bias, and combination of heterogeneous trials, which included adults and high-risk neonates, inadequate assessment of the effect of methodological quality on outcome, and the absence of a plausible mechanism to explain albumin-associated excess mortality [42, 43]. Moreover, the meta-analysis did not include burns trials in which the mortality rate was lower in albumin [44]. Finally, the crossover pattern in which the most seriously ill patients in the control group were switched to albumin as a rescue measure, therefore, would bias the pooled estimates of relative risk in favor of the control group [43]. Only a few years later, this meta-analysis was followed by an updated meta-analysis, in which 55 trials involving 3504 randomly assigned patients had been included and 525 deaths occurred [43]. Pooled relative risk estimates among trials with blinding and those with 100 or more patients were 0.73 (CI, 0.48–1.12) and 0.94 (CI, 0.77–1.14), respectively. The relative risk was also consistently less than 1.0 for trials that had two or more of the four attributes indicating

higher methodological quality such as blinding, mortality as an endpoint, no crossover, and 100 or more patients. These observations suggest that albumin therapy reduces mortality. Overall, the results of this meta-analysis supported the safety of albumin use in critically ill patients. In 2004, the results of the Saline versus Albumin Fluid Evaluation (SAFE) randomized control trial (RCT) in 7000 critically ill patients were published, showing that a 4% albumin solution was as safe as normal saline as resuscitative fluid in critically ill patients [45]. Furthermore, the subgroup analysis of the SAFE study showed benefit of using albumin in patients with severe sepsis, with an adjusted odds ratio (OR) for death of 0.71 (95% CI, 0.52–0.97; P = 0.03) for albumin compared with saline. Therefore, the authors concluded that administration of albumin compared to saline did not impair renal function or organ function and may have decreased the risk of death in patients with severe sepsis [1].

Moreover, Guidet and colleagues assessed the cost-effectiveness of albumin, as given in the SAFE study on patients with severe sepsis and septic shock, who were admitted to 1 of 35 French ICUs. Based on a presumed 4.6% reduction in mortality associated with albumin therapy as shown in the SAFE trial, 513 lives were saved among the 11,137 patients included, with an estimated life expectancy for each life saved of 9.8 years. Therefore, the authors suggested that albumin administration was a cost-effective intervention in patients with severe sepsis or septic shock [4].

In a subsequent meta-analysis that included 17 studies with randomized 1977 participants, there were eight studies that included only patients with sepsis and where patients were a subgroup of the study population. The use of albumin for resuscitation of patients with sepsis was associated with a reduced mortality, with the odds ratio of 0.82% (95% CI, 0.67–1.0, $P = 0.047$) [1]. Caironi and colleagues randomized 1818 patients with severe sepsis in 100 ICUs to receive either 20% albumin and crystalloid solution or crystalloid solution alone. During the first 7 days, patients in the albumin group had a higher mean arterial pressure and lower net fluid balance ($P < 0.001$). At 28 days the mortality rate was 31.8% in the albumin group and 32.0% in the crystalloid group. At 90 days the mortality rate was 41.1% in the albumin group and 43.6% in the crystalloid group. However, there was improved survival associated with albumin in patients with septic shock (1121 patients; 90-day mortality, 43.6% in the albumin group vs. 49.9% in the crystalloid group; relative risk 0.87; 95% CI, 0.77–0.99; $P = 0.03$) [46]. The results of a recent meta-analysis, which included 14 studies (18,916 patients with sepsis), showed that resuscitation with balanced crystalloids or albumin in patients with sepsis seems to be associated with reduced mortality [47]. Furthermore, the improved survival associated with albumin in patients with septic shock was confirmed in a recent meta-analysis. In this meta-analysis, 3658 with severe sepsis and 2180 with septic shock patients were included in the analysis [48]. Compared with crystalloid, a trend toward reduced 90-day mortality was observed in severe sepsis patients resuscitated with albumin (OR 0.88; 95% CI, 0.76–1.01; $P = 0.08$). However, in septic shock patients the use of albumin for resuscitation significantly decreased 90-day mortality (OR 0.81; 95% CI, 0.67–0.97; $P = 0.03$) [48].

Albumin resuscitation in sepsis has a unique feature compared to crystalloid as its effectiveness as a plasma-volume expander does not change in pathophysiological

conditions associated with increased microvascular permeability as sepsis. In addition, in severe sepsis the ratio of albumin to crystalloid for equal plasma volume expansion is approximately 1–4.5 [49]. The use of intravenous albumin in addition to antibiotics in patients with cirrhosis and spontaneous bacterial peritonitis reduced the incidence of renal impairment, death, and paracentesis-induced circulatory collapse in comparison with treatment with an antibiotic alone [50, 51]. In patients with acute respiratory distress syndrome, the use of albumin improved oxygenation but did not affect mortality [52].

The only exception for the benefit of using albumin in patients with sepsis was shown in the Fluid Expansion as Supportive Therapy (FEAST) trial as evidenced in increasing mortality with the use of albumin and saline boluses compared to no bolus (control group) in pediatric patients infected with malaria in eastern African countries. The bolus-therapy-induced hypervolemia by albumin and saline boluses in those patients could explain the increased mortality in this study compared to control group [53].

Albumin as a Neuroprotective Agent in Animal Experiments and Clinical Settings

Human serum albumin is a unique pleiotropic protein with neuroprotective properties. Rats received 2-h middle cerebral artery occlusion (MCAO) and were treated with human albumin or saline after 30 min of recirculation. The cortical blood vessels were examined afterward by laser-Doppler perfusion imaging (LDPI). Albumin therapy resulted in significant increases in arteriolar diameter, and reversing stagnation, thrombosis, and corpuscular adherence within cortical venules in the reperfusion phase after focal ischemia [54]. In a rat model of acute ischemic stroke induced by MCAO, rats received 1.25 g/kg intravenously at 2, 3, 4, or 5 h after onset of MCAO. Albumin therapy markedly improved neurological function, and reduced infarction volume and brain swelling [54]. The neuroprotective effects of albumin have been confirmed in a study with permanent MCAO in rats, where albumin treatment led to 48% increases in cortical perfusion ($P < 0.002$), but saline in the control group caused no change [54].

Moreover, functional magnetic resonance imaging (fMRI) was used to assess the albumin treatment during stroke recovery in rats. Albumin treatment was associated with restoration of fMRI response magnitudes and temporal profiles [55]. Rats underwent subarachnoid hemorrhage by endovascular perforation. Albumin of either 0.63 or 1.25 g/kg was injected immediately after the surgery. Albumin at low-to-moderate doses markedly improves long-term neurobehavioral sequelae after subarachnoid hemorrhage [56].

There are only two large published trials for the use of albumin after acute ischemic stroke and subarachnoid hemorrhage (SAH). In a randomized, double-blind, parallel-group multicenter trial in patients with acute ischemic stroke with a baseline National Institutes of Health Stroke Scale (NIHSS), 422 patients were randomly assigned to receive 25% albumin (2 g [8 mL] per kg; maximum 750 mL) and

419 to receive an equivalent volume of isotonic saline. The primary outcome was favorable, defined as either a modified Rankin scale score of 0 or 1, or an NIHSS score of 0 or 1, or both, at 90 days. The rate of favorable outcome did not differ between the groups. However, the patients in the albumin group had more mild-to-moderate pulmonary edema and symptomatic intracranial hemorrhage [57]. The reason for the negative outcome of this well-designed study was the high dose of albumin given as a single bolus, which might have induced those unfavorable effects and obscured the neuroprotective effect of albumin.

Albumin in the dose of 1.25 g/kg/day/7 days was tolerated by the patients with SAH without major complications and may be neuroprotective. Albumin in the dose of 1.25 g/kg/day/7 days had lower rates of cerebral vasospasm measured by transcranial Doppler (TCD), delayed cerebral ischemia (DCI), and cerebral infarctions. The main physiological effects of albumin treatment were elevation of the serum albumin concentration and mean arterial blood pressure. In addition, serum albumin remained elevated 7 days after treatment, which might be beneficial throughout the critical period of DCI [58, 59].

The mechanisms of the neuroprotective effects of albumin could be explained by its ability to attenuate brain edema and inhibit the endothelia cell apoptosis [60, 61]. Albumin administration may improve microcirculatory blood flow, increase organ perfusion, decrease leukocyte rolling and adherence, and reduce the inflammatory response [62]. Albumin preserves the blood brain barrier (BBB) by abolishing the hyperactivation of metalloproteinases-2 and -9 (MMP-2/9) following subarachnoid hemorrhage, suggesting MMP-2 and MMP-9 are key mediators for the albumin-induced neurovascular protection [56]. Moreover, albumin is considered the major antioxidant agent in the body. Albumin functions as an endogenous nitric oxide (NO) reservoir via binding of its sulfhydryl moiety of cysteine 34 residue with NO to form S-nitrosothiols (RSNO). It is worth mentioning that 82% of NO in blood is preserved in stable form as RSNO [14]. Therefore, albumin is able to neutralize the excessive circulating NO so as to prevent the nitro-oxidative stress and, on the other hand, to continue to release NO when the concentrations of low-molecular thiols are elevated. Thereby, albumin via RSNO-adducted NO can relax blood vessels, inhibit platelet aggregation, and increase aortic blood flow [56].

Albumin Use in Patients with Traumatic Brain Injury

In the SAFE trial, patients with traumatic brain injury (TBI) treated with albumin had worse outcomes than saline, most probably because the hypo-osmolar (4%) albumin solution with mean measured osmolarity of 266 (266–267) mOsm/kg H_2O used in the study induced increases in intracranial pressure but not the use of albumin per se [63, 64]. However, the use of 4 and 20% solutions in 93 patients with severe TBI and Glasgow Coma Score ≤ 8 in addition to a neutral or to a slightly negative fluid balance was associated with low mortality in those patients [65]. Therefore, the correct conclusion should be hypo-osmolar solutions should not be used in patients with TBI [66].

Albumin and Cardiac Surgery

The activation of systemic inflammatory and hemostatic systems that takes place during cardiopulmonary bypass (CPB) results in fibrin formation, platelet activation/consumption, and endothelial damage. However, the use of 5% albumin in priming the CPB machine has many advantages, such as preservation of oncotic pressure, preventing fibrinogen and platelet adhesion, and endothelial glycocalyx protection. In addition, it maintains the vascular barrier competency, prevents interstitial edema, and keeps the integrity of the microcirculation [67].

Oliver et al. compared 5% albumin priming with fresh frozen plasma (FFP)-based priming in pediatric patients [68]. Patients in the 5% albumin group had significantly lower administration of blood products. It was shown that using albumin for the priming volume, a dilution of coagulation factors is accepted during CPB. This will lead to less thrombin generation and consumption of coagulation factors and the FFP will be supplemented after protamine administration. However, the use of FFP as a priming solution will result in enhancing the thrombin formation during CPB, thereby more heparin is needed and more consumption of coagulation factors is triggered.

The use of albumin in priming the adult CPB may compete with fibrinogen in the formation of the protein layer coating the circuit and the oxygenator, and the preadsorption of albumin prevents fibrinogen adsorption and platelet adhesion. Russell et al. have shown in their meta-analysis that albumin compared with crystalloids as a priming solution exerts a number of beneficial effects, including platelet count and colloid osmotic preservation [69].

The use of albumin in the postoperative period after cardiac surgery has resulted in the preservation in clot formation time and maximum clot firmness. However, the use of low molar hydroxyethyl starch solutions (HES) (6% 200/0.5 or 130/0.4) resulted in prolongation in clot formation time and reduction in maximum clot firmness [70]. Moreover, the use of old high-molar HES and gelatin solutions correlated with the amount of postoperative bleeding after cardiac surgery, but the use of 4% albumin solution did not [71]. The same results have been confirmed in a meta-analysis comparing the use of HES solutions with albumin. Hemodynamics were similar in both groups, but the use of albumin decreased blood loss, the amount of blood products transfusions, and the need for reoperation postoperatively [72]. The presence of hypoalbuminemia (cutoff 18 g/L) after cardiac surgery was found to be a better predictor for mortality after cardiac surgery—even better than EUROscore [73]. In a recently published prospective, randomized, double-blind, placebo-controlled trial, the preemptive correction of a low preoperative albumin level by administering HSA in patients undergoing off-pump coronary artery bypass (OPCAB) is associated significant reduction in the incidence of AKI, from 26% in the control group to 13.7% in the albumin group. The editorial that accompanied the

study has suggested that restoring the target level is associated with reduction in AKI in amplitude greater than that of any known intervention in patients undergoing OPCAB [74, 75].

Albumin Solutions

Edwin Cohn's development of stable albumin solution during World War II was based on a fractionation scheme, which was rapidly adopted by a number of pharmaceutical companies. The pasteurization technique used in albumin solutions production is very effective in eliminating the risk for viral and bacterial infections. Moreover, the recent introduction of ion exchange chromatography in the production of albumin is very effective in reducing the risk of prion disease transmission by albumin solutions [76]. The use of albumin is considered safe practice; in a study evaluating adverse event reporting between 1998 and 2000, the incidence of all reported serious nonfatal and fatal adverse events was just five per million doses, and no patient death was classified as probably related to albumin administration [77].

Currently available human albumin solutions may differ in protein content and composition, binding capacity, metal ion content, antioxidants prosperities, and capacity to bind drugs [78]. It is noteworthy to mention that cysteine 34—the most important antioxidant residue in HSA—is oxidized in 23% of healthy human volunteers versus 54–60% in commercial preparations [79], which may influence the properties and hence the clinical impact of albumin solutions [80].

Albumin solutions are available in a variety of concentrations, mainly 20–25% or 4–5%. Iso-oncotic preparations of HSA are more effective than crystalloids solutions in maintaining the intravascular volume (>80% vs. <20%) [81]. Hypertonic albumin (20–25%) is used in patients with edema as it avoids excessive sodium and chloride loads [78]. Nevertheless, hypotonic 4% solutions should not be used in patients with traumatic brain injuries.

The excessive need for the HSA solutions has encouraged its production using recombinant DNA technology in both prokaryotic and eukaryotic hosts. HSA molecule structure is quite complicated; with 35 cysteine residues, 34 of them form disulfide bonds. Such complicated structure in this large recombinant protein could be a burden in both protein synthesis and folding system, which could result in the low expression or incorrect folding of recombinant HSA (rHSA). Recently, transgenic rice *Oryza sativa* has been used successfully as a novel bioreactor to produce sufficient quantities of safe rHSA. However, to establish appropriate impurity removal and detection methods in rHSA manufacturing remains a challenge (Fig. 10.4) [82, 83].

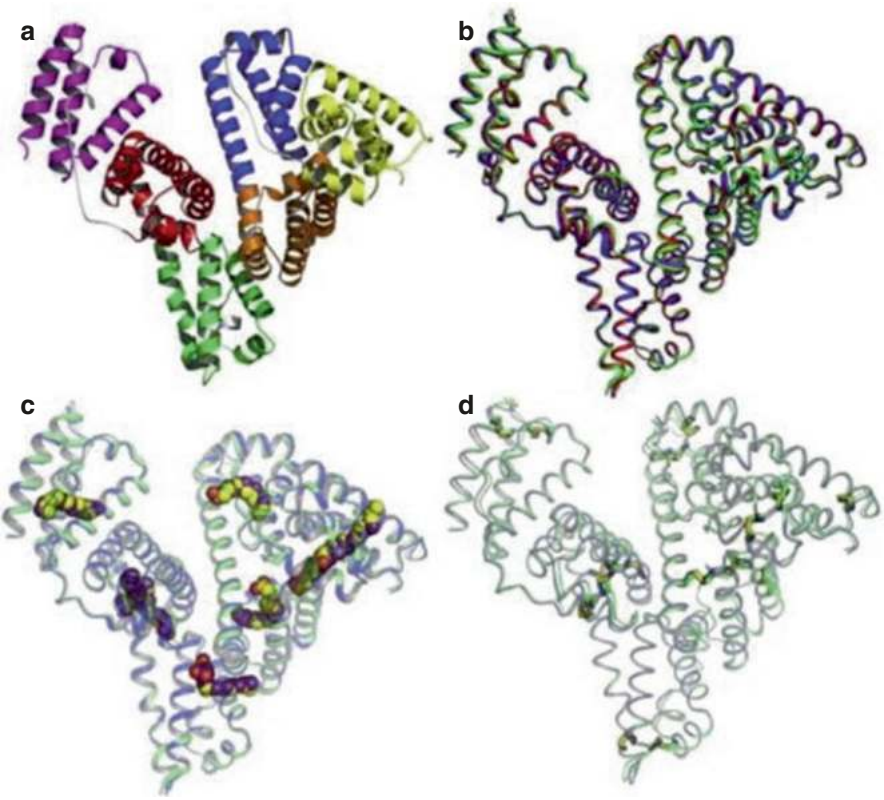

Fig. 10.4 Structures of rHSA from yeast and rice. (**a**) Overall structure of recombinant human serum albumin. (**b**) Comparison of recombinant HSA from rice (*green*, PDB: 3SQJ) or yeast (*blue*, PDB: 1E7G) to HSA from plasma (*red*, PDB: 2I2Z), the RMSDs of two rHSAs to pHSA were 0.605 and 0.374 Å, respectively. (**c**) Fatty acids binding in rHSAs. The fatty acids bound to rHSA from plant (*green*) and yeast (*blue*) were represented by sphere coloring as *yellow* and *brown*. (**d**) Disulfides in rHSA from yeast and rice. Disulfide bonds were shown as yellow sticks (Reprinted with permission from Chen et al. [82])

Conclusion

HSA has many physiological and biochemical properties that render its use relevant to many aspects of the disordered vascular and cellular functions. HSA has not yet showed all its secrets, and its benefits can only be realized by conducting clinical trials appropriately powered to relevant clinical endpoints.

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Albumin in the Critically Ill

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Abstract

Albumin continues to be one of the options for colloid resuscitation in critically ill patients despite limited evidence for its use. It does seem to have an advantage over other colloids with a better side-effect profile. With it's ability to increase intravascular oncotic pressure and other postulated metabolic benefits, albumin is preferred by many practioners worldwide for fluid resuscitation amongst ICU patients. In some studies outcome benefits have been shown, especially in patients with sepsis and post cardiac surgery patients. Limitations of its use are associated with its availability, cost and limited side-effect profile.

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Key Points

1. Albumin continues to be one of the main choices for colloid resuscitation amongst critically ill patients.
2. There is paucity of evidence supporting albumin as the mainstay of resuscitation except in sepsis and post-cardiac surgery patients.
3. Albumin use in traumatic brain injury patients has been associated with worse outcomes.
4. Cost and availability of albumin continues to be the predominant limiting factor for its use in critically ill patients.

Introduction

Fluid resuscitation is one of the key aspects of patient care in critically ill patients with absolute or relative hypovolemia. Other than cardiogenic shock, all other forms of shocks require fluid resuscitation or volume expansion. Debate about superiority of one type of fluid over another for resuscitation in this patient population has remained unsettled for most part despite decades of research [1]. Crystalloids still remain the main and initial fluids of choice for volume expansion to counteract hypovolemia. Colloids have been postulated to have significant benefit over crystalloid in resuscitation, as they are more likely to stay intravascular and for a longer period of time.

An international survey of preferred plasma volume expanders for critically ill patients showed significant variability in practice patterns across the world [2]. Except for dehydration and drug overdose, where initial resuscitation was chiefly using crystalloids, the majority (65%) of the survey respondents used a combination of both crystalloids and colloids for initial resuscitation. Colloids were preferred for resuscitation in patients with cirrhosis (42%), coagulation disorders (42%), or adult respiratory distress syndrome (39%). This is despite lack of any evidence for benefit in patients with ARDS along with some deleterious impact of colloid resuscitation amongst patients with coagulation disorders or resuscitation with starches [3]. First-line plasma expanders continue to be isotonic crystalloids (81%), starches (55%), gelatins (35%) whereas albumin (7%) found lower preference. There were regional practice variations also noted with colloids, especially gelatins (68%) alone being preferred more frequently in the United Kingdom (40%) whereas starches more so in Germany (81%) and The Netherlands (66%). The main factors behind preferences for first-line plasma volume expanders were time to volume loss correction, duration of effect, adverse events, and cost [2].

Critical Illness Pathophysiology and Resuscitation

The albumin concentration in plasma in healthy humans' ranges between 33 and 52 g/l. Human serum albumin accounts for about 60% of the total proteins and contributes to almost 80% of the intravascular oncotic pressure [4, 5] and has a

molecular weight of 66,500 Da. The ability of colloids to generate higher oncotic pressure has made them more attractive for resuscitation as they are thought to maintain a higher intravascular oncotic pressure and thus drive more volume intravascular rather than leaking into extravascular space.

Critical illness represents a complex pathophysiologic state with multiple system organ dysfunction, metabolic derangements and a response generated to correct these derangements. In critically ill patients after surgery and patients with sepsis there is altered permeability and increased transcapillary escape resulting in a disruption of this relationship [6] and in loss into spaces that do not contribute to the intravascular volume. Systemic inflammatory response syndrome (SIRS) and MODS (multiorgan dysfunction syndrome) are the hallmarks of this pathophysiologic state. In SIRS one is confronted with vasodilation and capillary leakage of fluid triggered by a cascading reactionary inflammatory response by various of cellular and non-cellular agents in a response to injury. This leads to relative intravascular hypovolemia due to vasodilation creating increasing capacity within the overall vascular space and leakage of fluid into the extravascular space due to capillary leakage. The movement of Human Serum Albumin (HSA) across the capillary wall is defined as the transcapillary escape rate (5% per hour), which indicates the percentage of intravascular HSA leaving the intravascular compartment per hour [7]. MODS also plays an important role in determining fluid balance of the patient as cardiac depression, acute kidney injury and other organ dysfunctions create significant fluid imbalance. Metabolic derangements compound the problem with acidosis, hyperglycemia and associated electrolyte imbalances create a milieu that can further complicate balance between intravascular and extravascular fluid balance.

Fluid resuscitation in these patients has been supported by early goal directed therapy, especially in sepsis, although components of the same has been challenged in the recent times [8, 9]. Restoration of intravascular volume status, improves blood flow and thereby delivery of oxygen to peripheral tissues. Improvement in blood pressure, central venous pressure, decrease in pulse volume variation and lactic acidosis are common measurements for fluid resuscitation in critically ill. Early restoration of fluid status using 30 ml/kg of crystalloid, assessment and follow up of lactate levels and application of vasopressors to restore perfusion to mean arterial pressure to at least 65 mm of Hg, while attaining cultures and appropriate source control including empiric antibiotics has been the main stay of resuscitation of critically ill patients with sepsis [10]. Similar goals with some clinical practice variations have been applied in other vasodilatory shock and hypo perfusion states.

Commercial Preparations of Albumin

Edwin Cohn in the 1940s developed a stable pooled albumin solution during World War II based on a fractionation technique, which was subsequently rapidly adopted by a number of pharmaceutical companies [11, 12]. HSA that is available today is primarily produced by cold ethanol fractionization technique first described by Cohn and then pasteurized for at least 10 h at >60 °C to eliminate the risk of viral

and bacterial infections. Multiple modifications and combinations of this method with chromatography have been described and readers are encouraged to visit the mini review article by Raoufinia et al. [13].

The excessive demand for the HSA solutions has encouraged its production using recombinant DNA technology in both prokaryotic and eukaryotic hosts. Recently, transgenic rice Oryza sativa has been used successfully as a novel bioreactor to produce sufficient quantities of safe rHSA [14].

With the advances made in the extraction and purification processes, the use of albumin is considered safe practice; in a study evaluating adverse event reporting between 1998 and 2000, the incidence of all reported serious nonfatal and fatal adverse events was 5.28 per 10^6 doses. For non-fatal serious adverse events, the observed incidence was 4.65 per 10^6 doses while the observed incidence of fatal serious adverse events possibly related to albumin was 0.185 per 10^6 doses though no patient death was classified as directly related to albumin administration [15].

Currently available human albumin solutions may differ in protein content and composition, binding capacity, metal ion content, antioxidants prosperities, and capacity to bind drugs [6]. Albumin solutions are available in a variety of concentrations as a 3.5–5% or as a hypertonic solution 20–25%. Hypertonic albumin (20–25%) is used in patients with edema as it avoids excessive sodium and chloride loads, and is able to deliver higher oncotic pressure with minimal volume load [16]. Hypotonic albumin preparations should not be used in patients with traumatic brain injury [17].

Albumin Advantages and Disadvantages: Where Is This Evidence?

In patients with acute and chronic illness, serum albumin concentration has been shown to inversely affect the mortality risk [18]. Albumin has also been shown to play an instrumental part in maintaining the integrity of the endothelial barrier [19], as an antioxidant [20, 21], and transporter of nitric oxide [20, 22, 23] and fatty acids and drugs.

(A) Albumin and interaction with other proteins

HSA may protect other proteins including hemoglobin, insulin, and immunoglobin from glycation in the early stages of diabetes due to its long half-life and its high concentrations compared to other proteins [24]. Similarly, patients with Obstructive sleep apnea may demonstrate an increased oxidative stress that can contribute to cardiovascular and metabolic morbidities due to decreased HSA antioxidant properties [25]. The irreversible damages associated with diabetes such as retinopathy, nephropathy, neuropathy, and coronary artery disease could also be attributed to reduced antioxidant properties of glycated HSA.

(B) Albumin and effects of acid-base balance and serum electrolytes

Irrespective of the type of fluid used, administration of large amounts of resuscitation fluids over a short period of time has been associated with the development of acid base imbalances [1–3, 8, 9]. Belloma et al. in 2006 looked at the effects of saline or albumin resuscitation on acid-base status and serum electrolytes [26]. They concluded that the volume of fluid administered is a much stronger predictor than the type of fluid and these were also influenced by illness severity and the passage of time [26].

(C) Albumin and effect on the coagulation system

HSA has anticoagulant and antithrombotic functions [27]. Therefore, the use of HSA might be very beneficial in cases with hypercoagulable conditions such as during the perioperative period.

Bellomo, R., et al. in 2009 looked at the Effects of saline or albumin resuscitation on standard coagulation tests [3] and concluded that administration of albumin or of larger fluid volumes is associated with a prolongation of APTT and in ICU patients, the choice and amount of resuscitation fluid may affect a routinely used coagulation test. A recent article by Rasmussen et al. in 2016 [28] confirmed that finding that administration of HSA does not increase the amount of blood loss, the need for blood transfusion but decreases coagulation competence during major surgery.

Albumin in Critical Care

The crystalloid versus colloid debate in critical care has spanned several decades. Some of the issue seems to stem around safety, efficacy and risk benefit ratio of colloids versus crystalloid use and the expense of albumin compared with the relatively lower cost to crystalloids. More than two decades ago, a postal survey conducted in 451 ICUs in Germany showed that no real protocols or standards existed for volume replacement therapy in these units, with a large variance in the kind of fluid used [29]. Several systematic reviews in the past had led to conflicting evidence as far as the safety and efficacy of albumin was concerned. A lot of these analytics compared colloids and crystalloids and used hydroxyethyl starch and related gelatins in the colloid group, certainly something that has over the years shown clear disadvantage in terms of organ system failure and renal injury. An important specific question is the use or utility of albumin during resuscitation of a septic/critically ill patient. The evidence to support this is minimal and no difference in all-cause mortality has been seen spread over several years of evidence. Despite this, albumin is a safe solution for this practice and no harm has been associated with its use either [30].

In 2004, Finfer and colleagues examined nearly 7000 patients in a multicenter, randomized, double blind trial to compare mortality and safety using saline or 4% albumin in a mixed ICU population. This landmark experiment, named the SAFE trial, still holds as the major weight of evidence when it comes to evaluating the usefulness of albumin resuscitation in the critically ill. The authors saw similar outcomes (death at 28 days, ICU days, hospital days, days on mechanical

ventilation, or days on renal replacement therapy) in both groups [31]. Subgroup analysis of the albumin-treated group revealed a trend towards decreased mortality in patients with septic shock, and a trend towards increased mortality in trauma patients, especially those with traumatic brain injury. This trial also forms the largest weight of evidence for a large Cochrane review that established no mortality benefit to albumin in either patients with hypovolemia or those with burns. The authors used data from 38 trials, and 10,842 patients and recommended further question into whether albumin use maybe indicated in select critically ill patients [18]. Annane and colleagues conducted the CRISTAL trial and used albumin and crystalloids in an open-label randomized manner in several ICUs in Europe, where they saw no significant difference in 28-day mortality. Amongst the nearly 1500 trial participants in either arm, there was a significance signal to improved 90-day mortality, and more days alive without mechanical ventilation, and without vasopressors, though these findings were regarded as exploratory and deserving of the need for further study [32]. Albumin use was associated with a higher chloride concentration during large volume resuscitation. The actual difference seemed minor compared to the volume of fluid, illness severity and duration of illness seemed to be a bigger driver of these outcomes [26]. Similarly, a post-hoc analysis of the SAFE trial showed a prolongation of coagulation time, with albumin resuscitation and larger volumes used for replacement [3]. Both 20% and 4% albumin were shown to be safe in healthy subjects, and was associated with an increase in stroke volume along with a reduction in afterload, compared with crystalloids [33]. Albumin has been previously used in combination with diuretic therapy and the combination seems to improve oxygenation, provide hemodynamic stability and achieve better negative fluid balance in patients with acute lung injury [34]. Although hypoalbuminemia is associated with increased mortality, use of albumin for volume resuscitation of critically ill patients with a serum albumin concentration ≤25 g/l is not associated with reductions in mortality, duration of ICU stay or mechanical ventilation, or in use of renal replacement therapy. Such practices, as 'routine" administration of albumin to 'build up' serum albumin in critically ill surgical patients in the ICU, is without evidence, and may not provide any clinical benefit whatsoever. Similarly, there is no substantive evidence to justify the use of hyperoncotic albumin solutions for resuscitation or supplementation in critically ill patients. An area of promise appears to be in the prevention of development and progression of pressure ulcers in the ICU [35].

Use of albumin for resuscitation has been guided chiefly by the SAFE trial and Cochrane analysis in the recent times [31]. A Cochrane analysis of use of human albumin solution for resuscitation and volume expansion in critically ill demonstrated important outcomes [18]. Importantly, overall estimates were influenced by the results of the SAFE trial, which contributed 75.2% of the information (based on the weights in the meta-analysis). The analysis demonstrated that for burns, the relative risk of death was 2.93 and for hypoalbuminemia the relative risk was 1.26. There was no substantial heterogeneity between trials in the various categories. The pooled relative risk of death with albumin administration was 1.05. Even in patient populations such as those with extensive fluid losses or hypoalbuminemia there has

not been any proven benefit of albumin resuscitation or colloid resuscitation. High cost is a significant issue since albumin is human derived and an expensive solution relative to crystalloids or even most of the colloids.

Albumin in Hypoalbuminemic States

Hypoalbuminemia is a very common finding in hospitalized and critically ill patients. Mechanisms that can contribute to this state can be decreased production (uncommon cause due to liver dysfunction), increased loss of albumin due to third spacing (as seen in sepsis and burns) or hemodilution due to use of large volume of crystalloids, or loss through the kidneys (as seen in chronic kidney disease and nephrotic syndrome), gastrointestinal tract (as seen in crohn's disease or increased lymphatic pressure) [36], loss of blood, or due to increased catabolism of albumin. Vincent et al. [37] in 2003 conducted a meta-analysis of 90 cohort studies with 291,433 patients looking at hypoalbuminemia as an outcome predictor and nine prospective controlled trials with 535 patients on correcting hypoalbuminemia and concluded that for every 10-g/l decline in serum albumin concentration, mortality was increased by 137%, morbidity by 89%, prolonged intensive care unit by 28%, hospital stay and 71%, resource utilization by 66% [37]. They also concluded that association between hypoalbuminemia and poor outcome appeared to be independent of both nutritional status and inflammation and complication rates may be reduced when the serum albumin level attained during albumin administration exceeds 30 g/l [37].

Albumin in Burns

There are multiple strategies that have been proposed for the fluid management in burn patients. Most have advocated different combinations of crystalloids, colloids, or plasma. A survey of the actual clinical practices of volume replacement regimen in burn patients in Europe was conducted in 2008. Sent out a total of 187 questionnaires consisting of 20 multiple-choice questions and the response rate was 43%. The answers came from a total of 20 European countries. They looked at the type of volume resuscitation, monitoring technique (use of CVP)use of PiCCO-system, and mixed-venous saturation datasets.

They concluded that there was no standardized therapy and the protocols differed widely among European burn units. They also found that the widely accepted importance of goal-directed therapy or data concerning use of albumin in the critically ill, have not yet influenced strategies of volume replacement in the burn patient [38].

Navickis, et al. in 2016 [39], conducted a metanalysis looking at recent data from both randomized and nonrandomized studies that evaluated the use of albumin and its effects on mortality and morbidity in adult patients. Randomized and nonrandomized controlled clinical studies were identified by computer database searches

and examination of journal contents and reference lists. The data that was extracted data were quantitatively combined by random-effects meta-analysis. A total of four randomized and four nonrandomized studies with 688 total adult patients were included. They found that the albumin infusion during the first 24 h showed no significant overall effect on mortality. However, when the studies that included high risk patients was excluded, use of albumin was associated with a reduction in mortality. Use of albumin also resulted in a lower incidence of compartment syndrome. They concluded that albumin can improve outcomes of burn shock resuscitation in some patients.

In general, hypertonic solutions, albumin, and plasma have been associated with lower volume requirements for initial resuscitation, lower intra-abdominal pressure, and a lower incidence of compartment syndrome [40].

Eljaiek et al. in 2017 [41] did a review the literature summarizing the effect on mortality of albumin compared to non-albumin solutions during the fluid resuscitation phase of burn injured patients with >20% body surface involvement. Data was collected by searching MEDLINE, EMBASE and CENTRAL and the content of Burns and Journal of Burn Care and Research. A total of 4 trials (out of 164) involving 140 patients met their inclusion criteria. They did not find any significant benefit of albumin solutions as resuscitation fluid on mortality in burn patients. They did find that the total volume of fluid infusion during the phase of resuscitation was lower in patients receiving albumin containing solution. They concluded that there was not enough data to demonstrated benefit on mortality in burn patients resuscitated acutely with albumin solutions.

Albumin After Neurological Insult

Human serum albumin is a unique pleiotropic protein with neuroprotective properties. Intravenous administration of albumin has been reported to ameliorate neuronal damage during the acute phase of stroke, to preserve the blood–brain barrier by abolishing the hyperactivation of metalloproteinases [42], contribute to stroke recovery via neuroprotective properties and improve microvascular hemodynamics and to exert proendothelial effects [43]. Albumin administration has been shown to improve microcirculatory blood flow, increase organ perfusion, decrease leukocyte rolling and adherence, and reduce the inflammatory response [44]. The mechanisms of the neuroprotective effects of albumin could be explained by its ability to serve as an antioxidant by serving as an endogenous NO reservoir [7] and attenuate brain edema and inhibit the endothelia cell apoptosis [45, 46].

Belayev et al. demonstrated this neuroprotective effect of albumin as compared to normal saline infusion in Rats following a 2-h middle cerebral artery occlusion (MCAO). They showed that while albumin therapy does not induce major increases in parenchymal perfusion, it resulted in significant increases in arteriolar diameter, and reversed the stagnation, thrombosis, and corpuscular adherence within cortical venules in the reperfusion phase after focal ischemia by laser-Doppler perfusion imaging (LDPI) [43]. Thus they demonstrated that albumin therapy markedly

improved neurological function, and reduced infarction volume and brain swelling by improved erythrocyte perfusion within the ischemic penumbra [43]. Kim et al. in 2007 looked at the therapeutic efficacy of albumin and its effects on the recovery of stimuli-induced cerebral hemodynamics using functional magnetic resonance imaging (fMRI) in a rat model [47]. They concluded that restoration of fMRI response magnitudes, temporal profiles, and correlations with structure may reveal the extent and specific traits of albumin treatment associated stroke recovery.

There are very few large published trials for the use of albumin after acute ischemic stroke and subarachnoid hemorrhage (SAH). In a randomized, double-blind, parallel-group multicenter trial in patients with acute ischemic stroke with a baseline National Institutes of Health Stroke Scale (NIHSS), 422 patients were randomly assigned to receive 25% albumin (2 g [8 ml] per kg; maximum 750 ml) and 419 to receive an equivalent volume of isotonic saline. The trial was stopped prematurely for futility after 841 participants were randomized. The primary outcome did not differ by treatment assignment (albumin, 44.1%; saline, 44.2%) at the end of the 90 ± 30 days of follow up. Secondary outcomes were also neutral. The main adverse event that occurred within 48 h of initialization of the treatment was mild-to-moderate pulmonary edema, which was more common with albumin (13.1%) than saline (1.2%), a rate consistent with that of albumin-treated subjects in the ALIAS Pilot Trial [48] and the Part 1 Trials [49]. The incidence of symptomatic intracranial hemorrhage within 24 h was also almost 2.4-folds higher with albumin (4.1%) as compared to saline (1.7%) [50] resulting in a higher (2.8-folds) risk of a larger parenchymal hemorrhage in the albumin treated group by CT.

In the ALIAS pilot trial, Albumin in doses ranging up to 1.25 g/kg/day for 7 days was tolerated by patients with subarachnoid hemorrhage without major complications and it was thought to be neuroprotective. They showed that Albumin in the dose of 1.25 g/kg/day for 7 days had lower rates of cerebral vasospasm measured by transcranial Doppler (TCD), delayed cerebral ischemia (DCI), and cerebral infarctions [51].

In the SAFE trial, patients with traumatic brain injury (TBI) treated with albumin had worse outcomes than saline, most probably because the hypo-osmolar (4%) albumin solution with mean measured osmolarity of 266. Van Aken et al. very eloquently showed that osmolality of an infusion solution rather than the colloid osmotic pressure per se represents the key determinant in the pathogenesis of cerebral edema formation [52].

Albumin in the Cardiovascular ICU

Cardio-pulmonary bypass (CPB) that is commonly used in patients undergoing routine and complex cardiovascular surgery triggers a systemic inflammatory response due to a combination of surgical trauma, activation of blood components in the extracorporeal circuit, endotoxin release, ischemia and reperfusion injury [53] resulting in fibrin formation, platelet activation/consumption, and endothelial damage [54]. This ultimately contributes to low grade fever, increased third spacing [55]

due to loss of endothelial integrity, hemodynamic instability, coagulopathy and sometimes leading to multiple organ failure and even death [53, 54]. Multiple attempts to mitigate these by off pump surgery, limiting the extracorporeal circuit, biocompatible coating, steroids etc. have failed to date. The use of 5% albumin in priming the CPB machine has many advantages, such as preservation of oncotic pressure, preventing fibrinogen and platelet adhesion, and endothelial glycocalyx protection. In addition, it maintains the vascular barrier competency, prevents interstitial edema, and keeps the integrity of the microcirculation [56].

Oliver et al. in 2003 compared 5% albumin priming with fresh frozen plasma (FFP)-based priming in pediatric patients [57]. In acyanotic, non-complex pediatric patients, use of 5% albumin in the prime as compared to use of FFP was associated with a significantly lower need of blood products. A post hoc analysis showed that cyanotic patients undergoing complex operations, use of fresh frozen plasma was associated with less blood loss.

The use of albumin in priming the adult CPB may compete with fibrinogen in the formation of the protein layer coating the circuit and the oxygenator, and the preadsorption of albumin prevents fibrinogen adsorption and platelet adhesion. In 2004 Russell et al. [58] conducted a meta-analysis which included 21 controlled studies with a total of 1346 patients and concluded that albumin prime preserves platelet counts and significantly reduced the on bypass drop in platelets count.

Golab et al. in 2011 assigned 70 children with body weight <10 kg into two groups [59]. One group received 0.5 g/kg albumin in the priming solution with the goal of maintaining colloid oncotic pressure (COP) >15 mmHg. The second group received 5% albumin in the priming solution to reach a COP > 18 mmHg. There was a comparable postoperative weight gain in both groups. Patients in the high-COP group had a shorter duration of mechanical ventilation, a higher platelet count, and higher levels of plasma lactate concentration at 24 h postoperatively.

The use of albumin in the postoperative period after cardiac surgery has resulted in the preservation in clot formation time and maximum clot firmness. However, the use of low molar hydroxyethyl starch solutions (HES) (6% 200/0.5 or 130/0.4) resulted in prolongation in clot formation time and reduction in maximum clot firmness [60].

Navickis et al. in 2012 conducted a meta-analysis looking at 18 trials with 970 total patients comparing the use of HES solutions with albumin. They conclude that the hemodynamics were similar in both groups, but the use of HES was associated with increased blood loss (33.3%), the need for packed cells (28.4%), fresh frozen plasma (30.6%), and platelet (29.8%) transfusions [61]. They did not find any differences in fluid balance, ventilator time, intensive care unit stay, or mortality.

An important finding that seemed to affect the postoperative outcome was the presence of hypoalbuminemia (cutoff 18 g/l) after cardiac surgery. Fritz et al. in 2003 found that a postoperative albumin of <18 g/l and a procalcitonin level of >2.5 ng/l are associated with a higher 28-day mortality after cardiac surgery. These were found to be better predictors than the EURO score in these patients [62].

In a recently published prospective, randomized, double-blind, placebo-controlled trial, the preemptive correction of a low preoperative albumin level by administering HSA in patients undergoing off-pump coronary artery bypass

(OPCAB) was associated with a significant reduction in the incidence of AKI, from 26% in the control group to 13.7% in the albumin group. The editorial that accompanied the study has suggested that restoring the target level is associated with reduction in AKI in amplitude greater than that of any known intervention in patients undergoing OPCAB [63, 64].

Efficacy and Safety of 20% Albumin as Compared to 5% Albumin

Recently, buffered salt solutions and 20% albumin (small volume resuscitation) have been advocated as an alternative fluid for intravenous resuscitation. In a randomized, double blind, cross over study of six healthy male subjects Bihari et al. compared the pulmonary and hemodynamic effects following intravenous administration of 30 ml/kg of 0.9% saline, Hartmann's solution and 4% albumin, and 6 ml/kg of 20% albumin (albumin dose equivalent). Pulmonary function tests (spirometry, ultrasound, impulse oscillometry, diffusion capacity, plethysmography), two/three-dimensional Doppler echocardiography, carotid applanation tonometry, blood gases, serum/urine markers of endothelial and kidney injury were measured before and after each fluid bolus. The colloids caused greater left atrial stretch, decrease in lung volumes and increase in diffusion capacity than the crystalloids, but without producing pulmonary edema. Stroke work increased proportionally to increase in preload with all four fluids, but the increase was more after colloid administration, associated with a reduction in afterload. The cardiac performance was increased mediated through a smaller volume of infusion when compared 4% albumin [33]. In addition, there was no evidence of interstitial pulmonary edema with 20% albumin, but there was an increase in Ang-1/Ang-2 ratio, which has been associated with endothelial integrity [33]. Albumin at 20% caused minimal disruption to serum electrolyte concentrations except for a decrease in calcium concentration [65].

A recent SWIPE (Small volume resuscitation With albumin in Intensivecare: Physiological Effects randomized trial compared resuscitation volume requirements, fluid balance, and biochemical and physiological efficacy of 20% albumin vs. 4–5% albumin for fluid resuscitation in ICU patients [16]. They demonstrated that the cumulative volume of resuscitation fluid at 48 h (primary outcome) was lower, peak albumin levels were higher but sodium and chloride levels lower with 20% albumin.

Limitations of Use of Albumin

The cost factors associated with albumin have been examined in great detail and assume even more importance when albumin does not seem to significantly decrease mortality. In a 1400 patient trial in a cardiac intensive care unit, a restrictive albumin use policy saved about $45,000 of wholesale costs savings per month without a change in clinical outcomes [66].

Colloids, including albumin are not without their own set of toxicities. Albumin has been associated in particular with intravascular volume overload and myocardial depression. Other toxic effects may include, but are not limited to dilutional coagulopathy, capillary leak especially in the setting of a systemic inflammatory syndrome, and anaphylactoid reactions [67].

Conclusion

Despite higher cost and limited evidence for use in critically ill patients, albumin continues to remain a colloid of choice for many across the world. Although postulated to reduce overall fluid balance in a patient and keep the fluid intravascular, repeated studies have not demonstrated such efficacy and improved outcomes. In the context of limited availability of other colloid options, chiefly due to their side effect profile, albumin continues to be accepted as one of the key resuscitative fluids currently and in the near future.

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The Dilemma for Using Hydroxyethyl Starch Solutions for Perioperative Fluid Management

12

Christiane S. Hartog and Konrad Reinhart

Abstract

Hydroxyethyl starch is a colloid plasma expander that has recently been restricted by the European Medicines Agency (EMA) following safety concerns in critically ill patients or in patients with sepsis (2013). The EMA restricted HES use in these patients but continues to allow its use in surgical and trauma patients who suffer from hypovolemia due to blood loss that cannot be corrected by crystalloids alone. Following drug utilisation studies which showed that HES continued to be used in patients with contraindications, EMA conducted a new revision and introduced new risk minimization measures in 2018 to reinforce existing restrictions. This narrative review explains the basis for initial approval of HES, the presumed action of HES as plasma expander, and the mechanisms of its adverse effects on coagulation and on extravascular tissue uptake, especially in the kidneys with resulting renal failure, and presents an overview of recent important studies with a focus on surgery and trauma. No definitive, large-scale randomized controlled trials with patient-relevant outcomes and long-term follow-up exist in this population. Existing studies provide no assurance of a lower risk of coagulopathy, mortality, or kidney failure than in other critically ill patients. There are sufficient data to suggest that HES has similar risks also in these patients and should therefore be avoided.

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Key Points

1. Colloid solutions are theoretically superior to crystalloids as plasma expansion fluids but in practice have failed to show a patient-relevant benefit.
2. The colloid hydroxyethyl starch (HES) has potentially severe side effects due to impairment of coagulation and extravascular uptake with resulting kidney or other organ failure.
3. Because HES was introduced in the 1970s before adequately designed clinical phase I-III trials were mandatory, no evidence from randomized controlled trials (RCTs) was generated until investigator-initiated trials in critical care and sepsis revealed dose-dependent adverse HES effects on the kidney and coagulation system.
4. The available studies in surgical patients and patients with severe trauma provide no assurance that these patients have a lower risk of adverse events than other critically ill patients.
5. The European Medicines Agency (EMA) decision to restrict HES use only in critical care and sepsis and to allow its continued use in surgery and trauma is controversial and creates a dilemma, because treating acute blood loss in surgical and trauma patients with a substance that has no benefit but increases risks such as coagulopathy or renal failure seems paradoxical.

Introduction

Current Situation

Hydroxyethyl starch (HES) is a colloid plasma expander that is licensed to treat clinical states of hypovolemia and used in a variety of clinical settings. Based on two reviews, the European Commission implemented a decision in 2013 that because of the risk of kidney injury and mortality, HES solutions should no longer be used in patients with sepsis or burn injuries or in critically ill patients, and restricted the use of HES to the treatment of hypovolemia due to acute blood loss when crystalloids alone are not considered sufficient (Box 12.1) [1].

Box 12.1 Restrictions to HES use issued by EMA 2013, confirmed in 2018: *Contraindications, warnings, and restrictions to HES use issued by EMA 2013* [2]

Contraindications

- Sepsis
- Burns
- Impaired renal function or renal replacement therapy
- Intracranial or cerebral hemorrhage

– Critically ill patients
– Hyperhydration
– Lung edema
– Dehydratation
– Severe coagulopathy
– Severe impairment of liver function

Restrictions

– HES solutions should only be used for the treatment of hypovolemia due to acute blood loss when crystalloids alone are not considered sufficient.
– There is a lack of robust long-term safety data in patients undergoing surgical procedures and in patients with trauma. The expected benefit of treatment should be carefully weighed against the uncertainties with regard to long-term safety, and other available treatment options should be considered.
– HES solutions should be used at the lowest effective dose for the shortest period of time. Treatment should be guided by continuous hemodynamic monitoring so that the infusion is stopped as soon as appropriate hemodynamic goals have been achieved.
– HES solutions are now contraindicated in patients with renal impairment or renal replacement therapy. The use of HES must be discontinued at the first sign of renal injury. An increased need for renal replacement therapy has been reported up to 90 days after HES administration. Patients' kidney function should be monitored after HES administration.
– HES solutions are contraindicated in severe coagulopathy. HES solutions should be discontinued at the first sign of coagulopathy. Blood coagulation parameters should be monitored carefully in case of repeated administration.

New risk minimization measures introduced in 2018

• Implementation of a controlled access program by manufacturing companies. Only accredited hospitals/centres will be supplied with these medicines. The accreditation would require that relevant healthcare professionals who prescribe or administer them receive mandatory training on their safe and effective use.
• Warning and reminders in the packaging insert
• Direct letter to healthcare professionals
• Request to manufacturers to conduct studies to check that only patients who should be treated with these medicines are receiving them. These studies are in addition to ongoing studies on benefits and risks of HES solutions in patients with trauma and those undergoing elective surgery

The European Commission also issued contraindications and warnings for the use of HES outside the intensive care unit (ICU). HES solutions are now contraindicated in patients with renal impairment or renal replacement therapy, severe liver function impairment, and in severe coagulopathy. The expected benefit of treatment should be carefully weighed against the uncertainties with regard to long-term safety, and other available treatment options should be considered. In order to minimize potential risks in these patients, HES solutions should be used at the lowest effective dose, not be used for more than 24 h, and patients' kidney function should be monitored after HES administration. The use of HES must be discontinued at the first sign of renal injury. Additional post-marketing studies are required in patients with trauma and in elective surgery [2]. Recommendations by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) were endorsed by the majority of PRAC; however, there was substantial controversy. Fourteen of 36 members disagreed with the majority decision, voted for complete suspension given the lack of proven clinical benefit and the absence of positive evidence to provide reassurance of safety evidence for harm in surgery or trauma (Box 12.2) [2].

In 2017, Public Citizen, a US-American nonprofit consumer advocacy organization with over 500,000 members, sent petition letters to the FDA and to EMA, requesting the ban of HES. In 2017, EMA initiated a third review process triggered by a request from Swedish regulators, citing drug use studies suggesting that the medicines continue to be used in prohibited populations. Based on all available evidence from stakeholders, the EMA PRAC Committee recommended to suspend HES. This recommendation was endorsed by the regulatory body representing the European Union (CMDh). However, some EU member states requested further revision, arguing concerns about unmet medical need and unregarded scientific or technical questions, inducing the EC to refer the recommendation back to the CMDh. The revised CMDh recommendation—restriction and new risk minimization measures (Box 12.1) - were issued in July 2018.

Box 12.2 Divergent Statement by the EMA PRAC Committee

Divergent Statement by the EMA PRAC Committee in 2013 [2]

- Without evidence to provide reassurance that patients will not be exposed to increased risk of mortality and renal injury by use of HES, and given the lack of data supporting a clinically relevant benefit, suspension of marketing authorizations for HES products in all patient populations remains appropriate to protect public health.
- The mechanism underlying the risks of renal injury and mortality observed with HES is not well understood, and therefore these should be considered to be potential risks in all patient groups.
- The available studies in elective surgery and trauma cannot provide reassurance of a lower risk than in septic and critically ill patients, or indeed exclude such a risk.

- There is an overlap between those patient groups where the benefit–risk balance of HES is judged to be negative (septic and critically ill patients), and the patients who will receive HES under the revised indication allowing use in patients with hypovolemia due to acute bleeding (e.g., including the trauma and perioperative settings).
- There is very limited evidence on the benefits and risks of hydroxethyl starch solutions for use in elective surgery and trauma. There is some evidence that the volume-sparing effect of HES relative to crystalloid solutions is less than 3- to 4-fold, and may be around 1.8-fold in some types of surgery. The data evaluating benefit in the perioperative setting and trauma setting do not adequately support a clinically relevant beneficial effect for HES.
- Alternative treatments are available in the form of crystalloids, and high-quality care is possible without the use of HES according to a survey of 391 ICUs worldwide conducted in 2010 [3], which showed no use of HES in the United States or Australia.
- The ability of the proposed risk minimization measures to sufficiently minimize the risks of HES is a concern. Data are lacking to identify an appropriate maximum dose, and expert advice is that there is no absolute "safe" lower dose below which there is no risk associated with HES administration. The recommendation to monitor renal function in patients for at least 90 days may not be an effective measure to minimize the risk of renal injury in all patients, as detection of worsening of renal function by monitoring may not be practical in patients who are discharged shortly after receiving HES. Furthermore, in emergency settings, it may be particularly difficult to evaluate patients for contraindications.

Approval of Hydroxyethyl Starch in 1971

HES first received regulatory approval for use in the United States in 1971. This was before regulatory requirements as we know them today were put into place, which call for efficacy and safety data from phase I, II, and III trials; these were installed only after 1978 following workup of the thalidomide disaster [4, 5]. According to the legislation current at that time, HES licensure was based on efficacy data—mainly systolic blood pressure measurements—from several small, uncontrolled observations of a total of 315 patients and volunteers with observation periods of 24 h or less [6]. Subsequently, modified HES solutions, for instance, the so-called "modern" tetrastarch HES 130/0.4, were granted regulatory approval based predominantly on data from the initial approval [7]. Although new HES products were regularly marketed as "improved" with "less side effects" [8], evidence for this assumption from large-scale randomized controlled trials with crystalloid control fluids was not provided [9, 10].

Dose Limits

The dose limits for HES are set arbitrarily and are not the results of dose-finding studies with adequate comparators. Initially, daily dose limits were set at 20 ml/kg in analogy to the dose limit for dextran, a synthetic colloid already in use when HES was introduced, with which HES was found to share the side effect of dose-dependent prolonged bleeding [7]. In 1999, after the Pharmacovigilance Francaise reported fatal bleeding complications after HES 200/0.6 in patients with subarachnoidal hemorrhage, a cumulative dose limit of 80 ml/kg was introduced in France for HES 200/0.6 and daily control of coagulation parameters was recommended for other HES solutions if they were administered over 4 days or in excess of 80 ml/kg [11, 12]. The dose threshold for 6% HES 200/0.5 in Europe was 33 ml/kg/day. For the new, supposedly "safer" HES 130/0.4, this ceiling was raised to 50 ml/kg, based on the outcomes of a volume-replacement study (HS-13-24-DE) that was never published [7]. In 2008, a pooled analysis [13] on blood loss comparing HES 200/0.5 and the new HES 130/0.4 revealed that the HS-13-24-DE study had identified more blood loss after the use of the newer starch, which may have been the reason not to publish the results. Following the EMA review in 2013, the daily dose limit for starches was reset to 30 ml/kg. Of note, no safe HES dose is known. The Australian Crystalloid versus Hydroxyethyl Starch Trial (CHEST) identified a significantly increased occurrence of renal failure requiring renal replacement therapy (RRT) at a daily average dose of 526 ± 425 ml HES 130/0.4, which corresponds to 7.5 ml/kg for a 70 kg patient [14].

Pharmacokinetic Properties of Hydroxyethyl Starch

Hydroxyethyl starches are carbohydrate polymers. Because unmodified starches are rapidly degraded and insoluble at neutral pH, HES solutions are modified by hydroxyethylation that takes place at the carbon atoms of the glucose subunit of the starch molecule, predominantly at the C2 and C6 carbon atoms, and replaces the hydroxyl groups at the C-atoms by hydroxyethyl groups. This achieves a greater spread of the glucose polymer branches, increases solubility, and decreases intravascular cleavage by the enzyme alpha-amylase [15, 16]. HES solutions are thus classified by their degree of molar substitution (DS), which describes the proportion of hydroxyethylation at the C atoms of the glucose unit and can range from 0.4 (40%) to 0.7 (70%). Accordingly, HES solutions are known as tetrastarches (DS 0.4), pentastarches (DS 0.5), hexastarches (DS 0.6), and hetastarches (DS 0.7).

HES solutions are also described by their mean molecular weight. Different HES solutions are classified by the weight average, which is reported in kiloDaltons (Mw) and can range between 70 and 670. There are currently about 30 different HES solutions on the market worldwide. Of note, HES are polydisperse solutions, meaning that they contain a mixture of molecules of different molecular weights. This is caused by the already existing molecular weight distribution of the starting material (starch) and the cleavage of glycosidic bonds during the hydrolysis process.

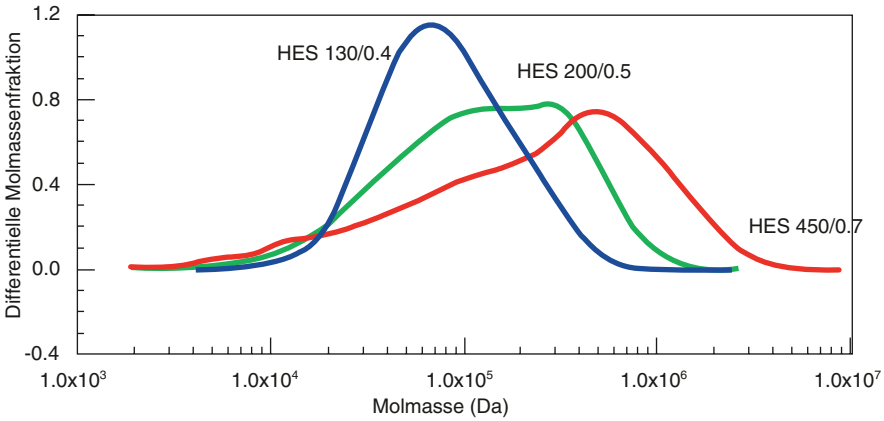

Fig. 12.1 Molecular size distribution in serum of rats after application of different HES solutions. This figure shows the distribution of molecular size in different HES solutions. All HES solutions are polydisperse and contain molecules of different sizes. The *x*-axis shows the molecular weights in Daltons, the *y*-axis shows the differential fraction of molecular sizes among each solution (Reprinted with permission from Wagenblast [16])

As Fig. 12.1 shows, all HES solutions contain varying molecular sizes from very small to very large molecules in the range of several hundreds of kiloDaltons. Thus, even in solutions with different means of molecular weights, for instance, the so-called "modern" tetrastarch solution (HES 130/0.4) and pentastarch (HES 200/0.5), the molecular weight distribution curves that describe the range of molecular sizes contained in the solutions may be quite similar [17]. These facts may explain that adverse effects of HES solutions are class effects that do not differ substantially between single solutions.

The Metabolic Fate of the Hydroxyethyl Starch Molecule

The metabolic fate of HES solutions is not well described. After infusion, HES molecules are cleared from plasma by renal elimination and tissue uptake [15, 18–20]. HES is not excreted through the feces [21]. Since only 40–65% of an infused dose could be recovered in the urine in humans, the remainder of the dose may be stored in the body [22]. Indeed, between 30 and 40% of administered HES solutions, regardless of their pharmacokinetic properties, are taken up transiently by tissue [23]. A recent systematic review included clinical studies that reported cumulative urinary excretion of HES over 24 h after infusions and plasma HES concentration at 24 h. Tissue uptake was computed as the difference between the infused dose and the sum of urinary excretion and residual plasma HES at 24 h and results were stratified by different HES solutions. Twenty-five clinical studies totaling 287 subjects were included. The 24-h tissue uptake was similar between different HES solutions, with 42.3% (95% confidence interval [CI] 39.6, 45.0) for low-molecular-weight HES (≤200 kDa) and 24.6% (CI 17.8, 31.4) for high-molecular-weight HES (>200 kDa) [24].

The uptake of HES into cells may alter their function. In cell cultures of human proximal tubular cells, application of HES 130/0.4 led to the ingestion of HES molecules into the cells and subsequent decrease of cell viability, which was not seen after application of crystalloids or low-dose albumin [25]. HES has been found in tissues of the reticuloendothelial system such as in kidneys, liver, spleen, and bone marrow. In 1998, Ginz et al. reported a case of a patient with sepsis who was treated with dextran (Mw 40,000 and 70,000 Da) and HES (Mw 450,000 Da, DS 0.7) for 5 weeks. Autopsy showed large colloid mass inclusions in parenchymal and reticuloendothelial cells of liver, lung, kidney, and spleen with altered organ morphology [26]. HES uptake has been reported in a wide variety of cell types, such as monocytes, macrophages, endothelium, renal epithelial cells, parenchymal liver cells, Schwann cells, and keratinocytes [24, 27], as well as in cells of the placenta [28]. HES storage in cutaneous nerve cells may cause severe and lasting pruritus [29–31].

Although HES is commonly administered to patients with severe and critical illness, most data on tissue uptake stem from studies in healthy volunteers. We have only scarce data on the metabolism of HES in severely sick patients and the long-term effects of HES tissue storage in patients. HES deposits are detectable for many months or years. Sirtl et al. studied 26 patients for up to 7 years after HES administration. Biopsies of the liver, muscle, spleen, intestine, or skin were studied using light and electron microscopy and immunohistochemistry. HES storage was detectable in all biopsies and was dose-dependent, decreased in all organs with time, and was greater in patients suffering from pruritus [32]. HES uptake into renal tubular cells appears as "osmotic nephrosis-like lesions" [33]. Pillebout et al. performed renal biopsies in patients who developed renal failure after liver transplantation. The authors found osmotic nephrotic lesions indicative of HES uptake as long as 10 years after its administration [34].

Transvascular Fluid Exchange and the Updated Starling Model

Colloids have long been believed to be more effective to achieve intravascular fluid expansion than crystalloids, based on the original model initially developed by Ernest Starling from experiments on the isolated hind limb of a dog. The original Starling model described fluid exchange as the product of differences between intra- and extracellular oncotic pressures and capillary permeability. However, the traditional form of Starling's principle has to be modified in light of insights into the role of interstitial fluid pressures and the lymphatic system, the recognition of the glycocalyx as the semipermeable layer of endothelium, local epithelial secretions in some specialized regions (e.g., kidney, intestinal mucosa), and standing plasma protein gradients within the intercellular cleft of continuous capillaries and around fenestrations. A more current explanation uses a two-pore system model where relatively small increases in large pore numbers dramatically increase fluid exchange during acute inflammation [35]. Colloid supporters have upheld that the demonstrated ineffectiveness of biophysical colloid therapy is due to damaged glycocalyx or capillary leakage, but according to new findings from fluid physiology—as Thomas Woodcock et al. have nicely explained in their well-researched paper on the glycocalyx model

of transvascular fluid exchange (see Chap. 8 of this book) [36]—colloid therapy is ineffective because the colloid osmotic pressure of plasma restricts but does not reverse the transendothelial fluid flux from capillary to interstitium. In particular, reabsorption of filtered fluid at the venous end of a nonfenestrated capillary is essentially insignificant for clinical considerations [37].

Hemodynamic Effects

Meta-analyses performed by the Cochrane Collaboration have consistently found that resuscitation with colloids is not associated with an improvement in survival, compared to resuscitation with crystalloids, in patients with trauma, burns, or following surgery [38]. These reviews have challenged the routine use of colloids, which are not beneficial but considerably more expensive than crystalloids. However, colloids and in particular starches were the preferred fluids in critical care [3]. The traditional understanding and one of the arguments used in favor of starches was that they were superior to crystalloids in increasing myocardial preload and intravascular volume. Indeed, colloids achieve a more rapid improvement in the hematocrit than crystalloids but this effect is transient [39]. The widely held belief that about fourfold or even higher volumes of crystalloid than colloid fluids are required to achieve hemodynamic stabilization has been challenged in the last years by large-scale fluid studies that compared crystalloid and colloid resuscitation. They showed crystalloid-to-colloid ratios between 1 and 1.45 (Fig. 12.2) [14, 39–45]. Thus, the volume-sparing effect of colloids is considerably lower than believed. A

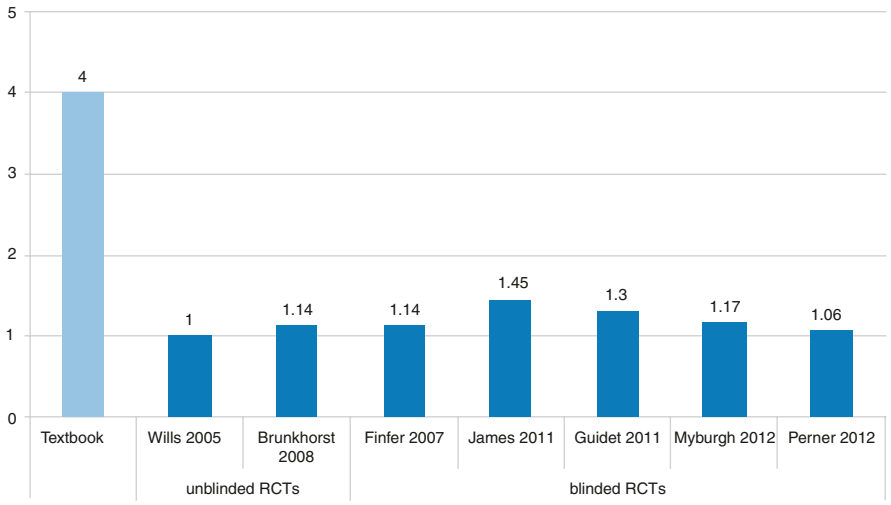

Fig. 12.2 Crystalloid-to-colloid ratios. While textbook knowledge based on theoretical arguments postulates a crystalloid-to-colloid ratio of 4 or higher, recent RCTs, among them five where study personnel were blinded to the nature of the administered fluid, found ratios between 1 and 1.45. The *y*-axis shows the ratio of crystalloid-to-colloid volumes that were administered to achieve preset hemodynamic endpoints in the respective studies [14, 39–45]

recent meta-analysis assessed the crystalloid/colloid ratio in studies comparing (any) crystalloid with (any) colloid in all types of patients. Twenty-four studies had sufficient data for meta-analysis. The crystalloid/colloid ratio across all the studies included in the meta-analysis was 1.5 (95% confidence interval [CI], 1.36–1.65) with marked heterogeneity among studies (I^2 = 94%). The authors stated that the crystalloid/colloid ratio had decreased over the years, but the main reasons behind the high heterogeneity among studies remain unclear [46].

The effect of colloids may be mitigated in critically ill or septic patients who may have increased capillary permeability. What is the fluid ratio in surgical patients? The effect of HES on cardiac surgical patients was prospectively assessed in a before-and-after study by Bayer et al., who compared a treatment period with HES against a treatment period in which only crystalloids were used; this study included 2137 patients in the HES period and 2017 in the crystalloid period. Shock reversal was similar in both periods: Time to vasopressor cessation, normalization of serum lactate, and mean arterial pressure did not differ among groups. Total fluid requirement was 163 ml/kg in the HES period and 224 ml/kg in the crystalloid period (ratio 1.37) with a higher fluid intake in the crystalloid group only during the first 20 h [47].

Do Patients Benefit from Hydroxyethyl Starch?

Does the advantage of requiring somewhat less fluids to achieve similar hemodynamic outcomes confer a patient-relevant advantage in clinical trials? No trial could yet show that patients benefitted from fluid resuscitation with HES, as observed consistently in the meta-analyses from the Cochrane Collaboration [38]. It is unclear how the presumed benefit of HES can be established. HES supporters [48] now argue that HES had not been given correctly in recent RCTs that showed negative effects after HES administration [14, 43] and that HES may still be beneficial if it were applied early, according to an algorithm, under observation of a maximum dose and in the absence of renal failure. The authors themselves concede that these arguments are speculative [48]. The discussion recalls similar arguments that were made to explain the negative findings from the first sepsis trials in France and Germany, suggesting that kidney failure might have been avoided by using newer starches and "watering the kidney" sufficiently with crystalloids [9].

To date, clinical trials have shown that HES is not beneficial in a variety of patient populations. The blinded RCT of 7000 ICU patients from the Australian and New Zealand Intensive Care Trials Group ANZICS found that 90-day mortality was not different (17% in the saline group vs. 18% in the HES 130/0.4 group) [14]. The recent large sepsis trials showed an excess mortality in the HES groups at 90 days [40, 43, 45] (discussed in more detail in the following section). In trauma, the first and blinded trial to compare HES with crystalloid showed excess mortality after 30 days, reported in a post hoc letter by the authors [41, 42]. Systematic reviews and meta-analyses of trials with surgical patients found no clinical benefit for patients receiving 6% HES solutions or alternative intravenous (IV) fluids (19 trials with

1567 patients) [49]. Hemodilution with HES was also not beneficial in indications outside critical care, for instance, in acute hearing loss [50], pre-eclampsia [51], postoperative nausea and vomiting [52], or postoperative fluid therapy to reduce surgical site infection [53]. Most recently, the FLASH multicenter randomized controlled trial, which assessed the effects of HES vs saline for fluid resuscitation in patients undergoing major abdominal surgery, found that the primary endpoint (a composite endpoint of death or major postoperative complications) occurred in 36% of patients (139/389) in the HES group vs 32% (125/386) in the saline group (absolute difference, 3.3%; 95% CI, −3.3% to 10.0%; P = .33) without significant difference but showed a trend favoring saline. Patients in the HES group received less study fluids on the day of surgery (median 500 mL) but had lower diuresis and a more positive fluid balance on day 2 [54].

Hydroxyethyl Starch Toxicity

Like other synthetic colloids, HES is associated with a range of adverse effects. The pathomechanisms of these effects are not fully explored. Bleeding impairment may result from interference with thrombocytes and coagulation factors [55, 56], while tissue storage resulting from the rapid accumulation of HES in tissues and macrophages [24] may be the most important mechanisms that influence morbidity and survival in susceptible patients in a dose-dependent manner. There has been some debate about whether molecular weight, substitution, or rather the cumulative dose plays a role and whether HES has different effects in surgical or trauma patients [8]. These questions will be addressed as follows.

Mortality

Critically ill and septic patients In 2008, the open-label Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial, which randomized septic patients to 10% HES 200/0.5 or Ringer's lactate, found a trend toward increased 90-day mortality in the HES group (41.0% vs. 33.9%, $P = 0.09$), with the rate of death being significantly increased among patients who received a higher dose of HES, as compared with those who received a lower dose (57.6% vs. 30.9%, $P < 0.001$) [40]. A subsequent blinded RCT with 804 septic patients by the Scandinavian Critical Care Trials Group compared HES 130/0.4 to Ringer's acetate and found an increased 90-day mortality rate in the HES group (51% vs. 43%, relative risk [RR], 1.17; CI 1.01–1.36; $P = 0.03$) [43]. The CHEST trial with 7000 ICU patients and a blinded comparison of HES 130/0.4 versus normal saline found that 18.0% in the HES group and 17.0% in the saline group died within 90 days (relative risk in the HES group, 1.06; CI 0.96–1.18; $P = 0.26$) [14].

The reason why these studies could show not only the lack of survival benefit, but also harmful effects after HES resuscitation was that these investigator-initiated trials had sufficiently large patient samples to detect effects in patient-relevant

outcomes such as renal failure or transfusion exposure. In addition, they had a long enough follow-up period of 90 days to detect effects that only become manifest after longer periods of time. When these trials were included in a meta-analysis by a Canadian group, which evaluated acutely ill patients from 28 HES solution trials, starches—regardless of degree of molar substitution or molecular weight—were associated with increased mortality among 10,290 patients (relative risk, 1.09; 95% CI, 1.2–1.17) and increased use of renal replacement therapy among 9258 patients (RR, 1.32; 95% CI, 1.15–1.50) [57].

Surgical and trauma patients In these patients, such large-scale RCTs have not yet been performed. Small studies not surprisingly are too small to detect an effect of HES therapy on ICU or mortality in populations where the given risk of mortality is low. However, even small studies may suggest harmful effects of HES on outcomes. One of the larger studies was performed by Skhirtladze et al., who randomized 240 patients undergoing elective colorectal surgery to receive up to 50 ml/kg per day of either 5% human albumin (HA), 6% HES 130/0.4, or Ringer's lactate (RL) as the main infusion fluid perioperatively. The 90-day mortality was 2.6% (2/76) in the HA group, 1.2% (1/81) in the HES group, and 0% (0/79) in the RL group [58]. There was also a significant difference in blood loss in favor of starch, which will be discussed later. Feldheiser et al. performed a double-blind RCT with a 90-day follow-up in 50 patients undergoing gynecological cancer who received either HES 130/0.4 or crystalloid; five deaths were reported in the HES group, while no subjects died in the crystalloid group ($P = 0.051$) [59]. James et al. performed a blinded RCT in 115 trauma patients [41]; 30-day mortality rates were 12/56 (21%) in the HES and 6/53 (11%) in the crystalloid group as explained in a letter by the authors [42]. In the FLASH trial, death at 14 days occured in 12/389 (3%) of patients receiving HES and in 6/386 (2%) of patients receiving saline [54].

Coagulopathy and Prolonged Bleeding

At the time HES was introduced in the 1970s, scientists were aware of the fact that synthetic colloids prolonged bleeding but the mechanisms were obscure. In 1975, Alexander performed a set of elegant experiments and could show that the hemostatic defect associated with the use of plasma substitutes such as dextran or HES is a form of induced von Willebrand disease or disseminated intravascular clotting, ensuing from precipitation and removal of von Willebrand factor, factors VIII and I, microcirculatory abnormality, and platelet malfunction [60]. A systematic review of the influence of tetrastarches on hemostasis as measured by viscoelastic device analysis found that HES 130/0.4 administration results in hypocoagulation characterized by the formation of a weaker and smaller clot [61].

In susceptible patients, administration of HES can lead to potentially fatal bleeding. In France, HES 200/0.6 received a warning label [11] after a pharmacovigilance study documented three cases of fatal cerebral hemorrhage among nine patients with subarachnoid hemorrhage and acquired von Willebrand syndrome

after HES exposure [12]. In the United States, the Food and Drug Administration (FDA) issued a warning label for HES in 2004 because of increased bleeding observed in cardiac surgical patients [62]. Evidence from several large-scale RCTs in critically ill and septic patients demonstrated that pentastarch as well as the new tetrastarch significantly increased the need for transfusion of blood products in these severely ill patients [14, 40, 43, 63].

Evidence from surgical trials is poor due to the lack of large-scale RCTs in this setting with the statistical power to detect differences in patient-relevant outcomes. However, published trials suggest increased blood loss and transfusion need after administration of HES. Skhirtladze et al. [58] compared the effects of 5% albumin, 6% HES 130/0.4, and Ringer's lactate on blood loss after cardiac surgery and found that 35% of RL patients required blood products, compared with 62% (HA) and 64% in the HES group ($P = 0.0003$). In the double-blind trial conducted by Yates et al., which compared 6% HES 130/0.4 with crystalloid in colorectal surgery, 20/84 (23.8%) of patients in the HES group received blood transfusions versus 10/88 (11.4%) of patients in the crystalloid group; that is, a doubling of events [64]. Rasmussen et al. randomized 16 patients to receive either 6% HES 130/0.4 or Ringer's lactate during major surgery; thrombelastography showed that HES dilution led to a reduced clot strength while blinded evaluation of blood loss was 2.2 l (range 0.5–5.0) in the HES versus 1.4 l (range 0.5–2.4) in the crystalloid group ($p < 0.038$) [65]. In a prospective, randomized, double-blinded study, Schramko et al. assigned 50 patients scheduled for complex cardiac surgery to receive either balanced 6% HES 130/0.42 or Ringer acetate solution for cardiopulmonary bypass (CPB) priming. Randomization was stopped prematurely after 35 randomized patients (19 in the HES and 16 in the Ringer groups) because of the published report where HES 130/0.42 was associated with impaired renal function. Effects on hemostasis and fluid balance were investigated. Patients in the HES group needed more blood and blood product transfusions [66]. A few other small RCTs that investigated the modern HES 130/0.4 found induced hypocoagulation [67–69] and increased the use of blood products [68], while other small RCTs described reduced transfusion after HES administration [70]. Overall, a recent meta-analysis on the impact of starches on blood loss in cardiac surgery found that HES in comparison to albumin increased blood loss, reoperation for bleeding, and blood product transfusion after cardiopulmonary bypass without evidence that these risks could be mitigated by lower molecular weight and substitution [71]. These findings are confirmed by the recent FLASH trials in abdominal surgery, where significantly more patients receiving HES than saline received transfusions during the surgical procedure (19% vs 12%; P = .003) [54].

Kidney Failure in Critically Ill and Mixed Populations

Renal impairment after HES may be due to a plurality of causes, including reabsorption of HES into proximal renal tubular cells, which lead to characteristic lesions called "osmotic nephrotic lesions" [33], or renal plugging due to hyperviscous

urine [72]. Huter et al. investigated HES-induced adverse effects on renal function using an isolated porcine renal perfusion model and crystalloid controls. They observed HES-induced impaired diuresis and sodium excretion and identified renal interstitial proliferation, macrophage infiltration, and tubular damage [73]. Neuhaus et al. found that application of HES 130/0.4, but not crystalloid, to cell-cultured human proximal renal tubular cells decreased cell viability significantly in a concentration-dependent manner [25]. Bruno et al. could show that these harmful effects on human proximal renal tubular cells correlated only with the total administered dose of HES molecules; molecular size, substitution, and origin of starch (cornstarch or potato starch) were not relevant [74]. Schick et al. induced sepsis in rats by cecal ligation and puncture and treated the animals with crystalloid or colloid solutions. After 24 h the kidneys of animals treated with HES or gelatin showed osmotic nephrotic lesions and an overall increased injury compared to kidney from animals treated with crystalloids [75].

Clinical reports of renal failure associated with HES administration were first noted in France in 1993 [76]. Subsequent observations noted a higher incidence of kidney transplant failure in donors resuscitated with HES [77]. This triggered an investigator-initiated prospective randomized trial published in 2001 that compared resuscitation with 6% HES against 3% gelatin and reported a significantly higher occurrence of acute kidney failure in the HES group [78]. In 2008 and 2012, three large multicenter investigator-initiated RCTs were published that demonstrated increased renal failure associated with HES 200/0.5 or HES 130/0.4 in critically ill and septic patients [14, 40, 43].

In 2013, a Cochrane Collaboration systematic review examined the effects of HES on kidney function compared to other fluid resuscitation therapies in different patient populations. The review included 42 studies (11,399 patients). Overall, there was a significant increase in the need for RRT in the HES-treated individuals compared to individuals treated with other fluid therapies (RR, 1.31, 95% CI, 1.16–1.49; 19 studies, 9857 patients) and the number with author-defined kidney failure (RR, 1.59, 95% CI, 1.26–2.00; 15 studies, 1361 patients). The RR of acute kidney injury (AKI) based on RIFLE-F (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease—Failure) criteria also showed an increased risk of AKI in individuals treated with HES products (RR, 1.14, 95% CI, 1.01–1.30; 15 studies, 8402 participants). No differences between subgroups for the RRT and RIFLE-F based outcomes were seen between sepsis versus nonsepsis patients, high Mw and DS versus low Mw and DS (≥200 kDa and >0.4 DS vs. 130 kDa and 0.4 DS) HES solutions, or high- versus low-dose treatments (i.e., ≥2 l vs. <2 l). The authors concluded that the current evidence suggests that all HES products increase the risk in AKI and RRT in all patient populations and a safe volume of any HES solution has yet to be determined [79]. A Canadian group evaluated the association of HES use with mortality and acute kidney injury in acutely ill patients from 28 HES solution trials. Starches, regardless of degree of molar substitution or molecular weight, were associated with increased use of renal replacement therapy among 9258 patients (RR, 1.32; 95% CI, 1.15–1.50) [57].

Kidney Failure in Surgical or Trauma Patients

The question whether HES administration in these patient populations impairs organ function cannot be definitively answered for lack of large randomized controlled trials with an adequate follow-up, but there is some strong suggestion that HES may also impair kidney function in these patients. Recently, the FLASH trial with abdominal surgical patients found that the pre-specified seondary endpoint AKI occurred significantly more often in the HES group (23%) than the saline group (17%, relative risk 1.36 (1.02–1.82, p = 0.04) [54]. To date, the results if this trial have not yet been included in meta-analyses. Feldheiser et al. performed a double-blind RCT with a 90-day follow-up in 50 patients undergoing gynecological cancer who received either HES 130/0.4 or crystalloid; however, not surprisingly given the small sample size, they found no difference in creatinine levels during the hospital stay [59]. James et al. randomized a total of 115 patients with blunt or perforated traumatic injuries to either HES 130/0.4 or crystalloids; 2/56 (3.6%) patients in the HES group and 3/53 patients in the crystalloid group (5.7%) received RRT; this effect was not significant given the small study sample [41]. Yates et al. assigned 202 medium- to high-risk patients undergoing colorectal surgery to receive either chloride-poor 6% HES 130/0.4 or Hartmann's. The number of patients with any predefined complications was 46% in the HES and 38% in the crystalloid group; among the complications, renal failure occurred in 4/104 in the HES versus 0/98 patients in the crystalloid group [64].

Several observational trials, which used statistical methods of adjustment, reported dose-dependent impact of HES administration on renal function. Rioux et al. retrospectively evaluated the risk of acute kidney injury by consensus criteria using pentastarch 10% (250 kDa, 0.45) in a random cohort of 563 cardiac surgical patients. Fifty-four (10%) patients developed AKI; pentastarch remained independently predictive of AKI, with an adjusted odds ratio per ml/kg of 1.08 (95% CI 1.04–1.12, $p = 0.001$). This risk was dose-dependent, and the optimal cutoff volume predicting AKI was 14 ml/kg [80]. Kashy et al. evaluated the data of adults without preexisting kidney failure who had inpatient noncardiac surgery from 2005 to 2012. Among a total of 29,360 patients and after controlling for potential confounding variables, the odds of developing a more serious level of AKI with Hextend (HES 450/0.7) was 21% (6–38%) greater than with crystalloid only ($P = 0.001$) and increased as a function of colloid volume ($P < 0.001$) [81]. Bayer et al. analyzed a prospective observational cohort of 6478 consecutive patients with cardiopulmonary bypass surgery and found that renal replacement therapy was more common during periods when patients received synthetic colloids compared to only crystalloids. Risk of renal replacement therapy was greater after HES (mostly HES 130/0.4, odds ratio, 2.29; 95% CI 1.47–3.60) and gelatin (odds ratio, 2.75; 95% CI, 1.84–4.16; both $p < 0.001$) compared to crystalloid. Propensity score stratification confirmed greater use of RRT in the HES and gelatin periods compared to the crystalloid period (odds ratio, 1.46 [1.08, 1.97]; $p = 0.013$ and odds ratio, 1.72 [1.33, 2.24]; $p < 0.001$, respectively) [47]. Opperer et al. retrospectively assessed data from 510 different hospitals across the United States with 1,051,441 patients undergoing

elective total hip and knee arthroplasty and compared outcomes in patients who never received any colloid with those who received 6% HES or 5% albumin. Perioperative fluid resuscitation with HES was associated with an increased risk of acute renal failure (adjusted odds ratio 1.23 [95% CI 1.13–1.34]), cardiac complications (OR 1.22 [1.13–1.31]), pulmonary complications (OR 1.22 [1.11–1.33]), and intensive care unit admission (OR 1.53 [1.45–1.60]) [82].

A current and extensive meta-analysis compared the effect of HES with non-HES control fluid in adult surgical patients on renal replacement therapy (RRT) including 15 randomized trials with a total of 4409 surgical patients. HES significantly increased recourse to RRT, with a pooled relative risk of 1.44 and 95% CI of 1.04–2.01. The absolute risk increase of recourse to RRT attributable to HES was 1.2% (95% CI: 0.1–2.2%), indicating a number needed to treat with HES of 85 to prompt RRT in 1 additional patient. In a subset of trials comparing HES 130/0.4 with crystalloid, the pooled RR for recourse to RRT (1.47; 95% CI: 1.02–2.12) coincided closely with the overall pooled RR of 1.44 [83].

On the other hand, some selective meta-analyses that were funded or initiated by HES manufacturers have come to the conclusion that HES administration in surgery has no side effects. Jacob et al. published a meta-analysis on side effects of HES in cardiac surgery, which was commissioned by an HES manufacturer, and concluded that no safety issues could be identified in terms of blood loss, transfusion requirements, or hospital length of stay [84]. However, a number of methodological concerns have been pointed out in critical letters [85, 86]: lack of assessment of bias, which was identifiable in 65% of included trials; severe confounders that should have led to exclusion of included trials, for instance, because of considerable use of HES in the control arms in seven trials or concomitant use of albumin in the HES group in six trials that may have mitigated the effects; use of false data thereby inflating the blood loss difference in one trial by 2.3-fold; omission of data from four trials that all showed increased bleeding attributable to HES; omission of data from an unpublished trial that showed high blood loss in the tetrastarch group, which had been included in previous meta-analyses; and aggregation of intra- with postoperative blood loss and preferential use of calculated rather than measured blood loss, which all confounded the estimation [85, 86]. Another severely flawed meta-analysis was published by van der Linden et al., which concluded that HES 130/0.4 was safe in surgery [87]. This analysis was funded by an HES manufacturer and conducted by a public relations firm. It ignored unfavorable data from several randomized controlled trials but included study data from two trials that had an unlabeled artificial oxygen carrier solution as control, as was pointed by Takala et al. [88].

Liver Dysfunction and Hydroxyethyl Starch Storage Disease

Storage of HES after infusion was reported in liver [19]; repeated infusions in patients with chronic liver disease led to worsening of liver function and diffuse microvacuolization of Kupffer cells in liver biopsies [89]. In the CHEST trial, which randomized 7000 ICU patients to either HES 130/0.4 or saline, patients in the HES

group had an increased risk of new hepatic dysfunction, reported as increased risk for hepatic SOFA subscore (RR 1.56; 95% CI 1.03–2.36, $p = 0.03$) [14]. HES was also detected in placenta [28], in lung, kidney, and spleen with altered organ morphology [26], and in the kidney after as long as 6 years [34]. HES may also affect the brain; a follow-up of patients from a randomized controlled sepsis trial who received HES revealed worse scores on the mental health portion of the quality-of-life questionnaire than patients who had received crystalloids [90]. Repeated HES administration, for instance, during plasmapheresis, may lead to an acquired lysosomal storage disease [91] and storage of HES in bone marrow and liver may result in persistent thrombocytopenia and liver dysfunction [92].

Pruritus can develop as a result from HES storage. The dermatologist Stander et al. identified the origin of HES-related itching as a deposit of the molecule in skin nerves [31]. A retrospective study by her group found that the median latency between HES exposure and pruritus onset was 3 weeks, and the median duration of pruritus was 6 months. Pruritus was severe, or very severe, in 80% of patients. Although the median cumulative dose of HES was 300 g, 15% of patients developed pruritus after only 30 g. The authors could find no significant differences between HES 130/0.4 and HES 200/0.5 in pruritus latency, duration, or severity and concluded that HES-induced pruritus may occur at any dose, molecular weight, or substitution [30]. In the CHEST trial with 7000 ICU patients, pruritus occurred in 4% of patients in the HES group and in 2.2% of patients in the crystalloid group [14].

Quality of Life After Sepsis

Wittbrodt et al. performed a post hoc analysis of Danish survivors ($n = 295$) from a large-scale, double-blinded randomized controlled trial that compared tetrastarch with crystalloids for fluid resuscitation in sepsis. Median 14 months (interquartile range 10–18) after randomization, 182 (61%) and 185 (62%) completed questionnaires were obtained. Patients in the HES group scored worse in bodily pain and 49% of patients allocated to HES had experienced pruritus at any time after ICU discharge compared to 43% of those allocated to Ringer's (RR 1.13, 95% CI 0.83–1.55, $P = 0.43$) [90].

Pediatric Patients

Clinical studies in pediatric patients are small and inconclusive. However, a very recent meta-analysis of RCTs involved pediatric patients who received 6% low-molecular-weight (130 and 200 kDa) HES and finally included a total of 13 RCTs involving 1156 patients [93]. Trial quality was overall low. In comparison to other fluids, HES did not significantly decrease the mortality (RR = −0.01; 95% CI: −0.05 to 0.03; $P = 0.54$) and blood loss (mean difference [82] = 17.72; 95% CI: −41.27 to 5.82; $P = 0.10$). There was a trend toward increased creatinine levels in the HES group (MD = 1.81; 95% CI: −0.35 to 3.98; $P = 0.10$). HES significantly decreased the blood

platelet count (MD = 20.99; 95% CI: −32.08 to −9.90; $P = 0.0002$) and increased the length of ICU stay (MD = 0.94; 95% CI: 0.18–1.70; $P = 0.02$). The authors concluded that volume expansion with 6% HES significantly decreased the platelet count and increased the length of ICU stay, and might have an adverse effect on renal function [93]. In the absence of manifest clinical benefit, and given the documented risks, administration of HES in pediatric patients seems not to be indicated.

The Dilemma

The December 2013 European Union (EU) regulation created a dilemma which the recent decision in July 2018 has not solved. In member countries such as the United Kingdom and Italy, national medical authorities had removed the product based on concerns for patient safety, but must now, according to regulations, reintroduce HES against the recommendation of their national societies. In addition, the EMA requested two post-marketing studies in perioperative and trauma patients with which it may prove difficult to comply. Clinicians who believe—as did a considerable proportion of the EMA review board (Box 12.2) [2]—that the safety of HES is not reliably established in the patients, may not want to administer HES and patients who are fully informed might not want to receive a drug proven harmful in some settings with no reason to suggest a different effect in elective surgery or trauma patients. The available studies in these populations provide no assurance of a lower risk of mortality and kidney failure than in critically ill patients, nor were there any new studies in such patients to justify the revised decision. Moreover, the recent FLASH trial in abdominal surgery - the largest RCT to date with over 700 patients - confirms previous concerns by demonstrating a lack of benefit for the patient but additional harm including increased blood loss, more AKI and a trend towards higher mortality after HES [54]. Thus, treating acute blood loss in surgical and trauma patients with a substance that increases coagulopathy and is also otherwise harmful seems paradoxical. Lastly, lack of relevant benefit in trauma patients—and a nominally 10% higher mortality rate—was demonstrated in the first RCT [42] and in one retrospective study [94]. In the perioperative setting, the only RCT assessing a 90-day survival endpoint found a higher mortality rate using HES (0 vs. 5 patients died, $p = 0.051$) [59]. Moreover, no safe dose for HES has been defined [79]. Kidney failure occurred in intensive care patients after a mean dose of 7.5 ml/kg/day, a fraction of the maximal dose of 30 ml/kg of HES that is now applicable according to current legislation [14].

Conclusion

Without evidence to provide reassurance that patients will not be exposed to increased risk of mortality and renal injury by use of HES, and given the lack of data supporting a clinically relevant benefit, suspension of marketing authorizations for HES products in all patient populations remains appropriate to protect public health. Use of HES in surgical or trauma patients is not formally restricted according to the

2013 and 2018 European Commission majority decision, but this decision is questionable. HES side effects regarding bleeding impairment and kidney failure have been reported in all patient populations and significant risks are detected in well-performed meta-analyses also in surgical populations. HES is more expensive than crystalloids and high-quality care is possible without its use. There is no compelling reason to use it in surgical or trauma patients.

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Balanced Versus Unbalanced Salt Solutions in the Perioperative Period

13

Sheldon Magder

Abstract

Unlike organic electrolytes elements in the blood, such as sodium (Na^+) and chloride (Cl^-) ion, cannot be metabolized and their concentrations thus are dependent upon absorption and excretion. Cl^- concentration is on average 40 mEq/L less than that of Na^+ and this difference is an important determinant of hydrogen ion (H^+) concentration in blood (i.e. pH). Increasing Cl^- concentration produces acidemia and potentially effects renal, gastrointestinal, immune, and coagulation functions. There thus has been increasing interest in the use of intravenous solutions that avoid raising Cl^- concentrations. To do so requires anions besides Cl^- to "balance" the charge from Na^+. The major anions used are bicarbonate, lactate, acetate, and gluconate. The physiological actions of these electrolytes have been well described but the evidence of a clinical benefit is very limited. Large observational studies demonstrated potential benefits of low Cl^- solutions on renal function, hospital survival and reduction of infections. However, the evidence is more limited in randomized trials. Limitations of these trial have been that the amount of fluid given was not large and the populations were was generally low risk so the power to detect harm was low. It is unlikely that a pragmatic trial will be helpful and future studies will need to target subjects who are expected to receive large volumes of resuscitations fluid and who have risk factors that may make them less able to handle large Cl^- loads such as diabetics, subjects with large extracellular volume, recent intravenous contrast, periods of hypotension, and use of catecholamines. More specific end-points besides renal function also need to be considered such as gastrointestinal function, rate of infections, red cell survival and coagulation. Based on current evidence, survival studies would likely require very large sample sizes with subjects at increased risk.

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Key points

- To understand the potential harm from hyperchloremic acidosis it is necessary understand the physiological and chemical implications of elements in body solutions
- Na^+ is the major element for regulation of osmolality and Cl^- is the major element for physiological regulation of H^+ in the body.
- Although Cl^- plays a major role in regulating H^+, there is no good evidence to date that balanced solutions alter clinical outcome but there also are no definitive studies.
- Future studies need to target high risk patients including those receiving large volumes and those with underlying renal tubular dysfunction such as diabetics.
- End-points should focus on renal, gastro-intestinal dysfunction infectious and hematological adverse events.
- Distinction needs to be made between the concentration of Cl^- and total body Cl^-.

There continues to be interest in use of balanced salt solutions for fluid maintenance and resuscitation in critically ill patients [1–5]. The term "balanced" salt solution is used in different ways but in the clinical context it primarily is used to describe solutions in which chloride ion (Cl^-) is less than the sodium ion (Na^+). To understand why elements, and these elements in particular, play such an important role in biological solutions, it is helpful to understand their role in evolutionary development of living organisms, and the specific physiological actions of Cl^-. Next I will consider possible substitutes for chloride ions (Cl^-) in resuscitation and maintenance fluids. Finally, I will review current clinical data on the use of balance salt solutions. At the time of the previous version of this chapter, there were limited high level clinical studies, but there are now a few large randomized trials that have tested the benefit of lower Cl^- solutions. A central thesis of the previous chapter was that to detect a harm signal from excess use of Cl^-, clinical studies need to take into account the underlying physiological actions of the components of infused fluids, and target patients at greatest risk. Unfortunately, these still remain a weakness in recent studies. Some of these ideas have been previously reviewed [5, 6].

What Is a Balanced Salt Solution?

Major medical dictionaries do not give a definition for this term. An online site defined a balanced salt solution as one that provides water, normal concentrations of elements and inorganic ions, while maintaining a physiological pH and osmotic pressure [7].

In a Google search for balanced salt solutions, ophthalmic solutions and culture media came out high on the list of sites, as well as one of my slide presentation! A lot of fun as been made of the term "normal" saline because it is said that this solution is anything but like normal plasma [3], but "normal" is used to connote isotonic to normal plasma. From a practical point of view, in contrast to the simple isotonic

Table 13.1 Composition of common intravenous solutions

		Normal Saline	Lactated Ringer	Hartman's	Plasma-Lyte-148
Cations	Sodium	154	130	131	140
	Potassium	–	4	5	5
	Calcium	–	3	4	–
	Magnesium	–	–	–	3
Anions	Chloride	154	109	111	98
	Lactate	–	28	29	–
	Acetate	–	–	–	27
	Gluconate	–	–	–	23
	Osmolality	308	274	280	293

All values are Eq/L

normal (0.9%) saline solution, balanced salt solutions contain elements besides sodium (Na^+) and chloride (Cl^-) as well as inorganic molecules that are normally found in bodily fluids. Accordingly, these solutions also are called physiological fluids (Table 13.1). A concern with the use of just (0.9%) saline is that it increases the amount of Cl^- relative to Na^+ in the body. The addition of other negatively charged electrolytes to the solution allows for a lower concentration of Cl^- so that these solutions also are called low Cl^- solutions [8]. To understand the significance of the addition of inorganic electrolytes, the potential advantage of having a lower (Cl^-) concentration than that of isotonic saline, and why use the term "balanced", it is necessary to understand the central role of atomic elements in bodily fluids.

Importance of Atomic Elements in Bodily Solutions: An Evolutionary Story

Osmolality is the property of a solution that is based on the concentration of substances dissolved in the solution, which means that they form structures with water. The energy associated with being in solution is called osmotic pressure, and it creates the major force that regulates the amount of water in the body. This is measured as the force that will drag water across a membrane that is impermeable to a substance that has a concentration difference between two sides of a membrane. One milliosmole produces a pressure of 19.34 mmHg. As a point of clarification, it is not the molar concentration of the substance that counts, but rather its activity. This is because above a very low concentration of a dissolved substance, other components of the solution interact with it and decrease the force predicted from the concentration of the substance. Activity is in equivalents per litre (Eq/L) and this unit will be used for concentrations throughout this paper.

Osmolar force is determined by the molar concentration of a substance and not its size. Thus a 23 MW Na^+ ion has the same osmotic effect as a 69 kDa albumin molecule. Because elements cannot be metabolized, their concentrations in organisms only can be altered by absorption or excretion. Thus Na^+, Cl^-, potassium ion (K^+), calcium ion (Ca^{2+}), and magnesium ion (Mg^{2+}) have key roles in regulating the

osmolality of bodily solutions. Na^+ is the most common element in sea water and early on in evolution regulation of Na^+ concentration became the primary process for regulating the amount of water in organisms [9].

Water moves across membranes from areas of low concentration to areas of high concentration of electrolytes by osmosis. The force driving this are based on the general principle of thermodynamics that systems try to decrease order (increase entropy). This is the basis of what is called the principle of iso-osmolality, which says that all bodily compartments have approximately the same osmolality [10]. Elements themselves do not readily cross membranes, but they are moved through channels and exchangers down concentration gradients.

Current sea water is on average approximately 3% salt, but when life began it only was 1%. This still is the average salt concentration in the fluids of most organisms. This is because solubility of components of biological solutions, and the tertiary structures of large molecules, are very much affected by a solution's osmolality. Evolutionary processes build organic molecules based on earlier structures and so the background environment cannot change much. Thus, maintenance of intracellular osmolality at the level of the original sea level became important from an early evolutionary stage. Accordingly, osmolality has remained in the 280–310 mOsm/L range.

Bacteria, fungi, and plants have rigid walls that protect their intracellular volume and contents. Eukaryotic cells developed flexible membranes that gave them the advantage of being more mobile. Initial species were suspended in the sea and could readily exchange fluid and electrolytes across their cell membranes by diffusion and by active transporters [11]. This worked fine when these organisms lived in areas with large volumes of water at relatively constant concentrations, but without mechanisms to regulate intracellular osmolality eukaryotic cells would swell if the outside osmolality decreased and shrink if the outside became more concentrated. This would have limited the ability of early organisms to move to new areas to obtain essential nutrients. Furthermore, as cell walls became more complex, and developed imbedded proteins for regulating intracellular metabolism, cell volume needed to be tightly regulated to avoid damaging proteins tethered in the lipid membranes. Regulation of cell volume would have become even more important when the organism became multicellular because the increased diffusion distance created differences between cells at the centre compared to cells on the surface of the organism. Maintenance of constant cell volume was solved by replacing the Na^+ inside cells with potassium ion (K^+). This allowed cell volume to be regulated independently of the extracellular space, whether the outside of the cell was sea water or an interstitial space. K^+ is situated below Na^+ in the periodic table and thus has properties close to those of Na^+. K^+ also is the sixth most common element in sea water. With the development of specialized proteins to control the influx and efflux of Na^+ and K^+, the cell could maintain constant intracellular concentrations of these elements in the face of varying outside concentrations. In multicellular organism, the extracellular space, too, could be protected from the outside of the organism by having an outer membrane that allows minimal diffusion (i.e. skin), and regulating the absorption and excretion of fluid through a designated intake system (gastrointestinal tract) and excretory pathways (urinary system).

The development of specialized membrane proteins that maintain differences in the intracellular and extracellular concentrations of K^+ and Na^+ provided two important forces that can be harnessed to regulate intracellular functions [12–14]. Their concentration differences between inside and outside cells creates a force for diffusion which tries to equilibrate the two concentrations. Secondly, concentration differences across cell membranes produce charge gradients and this electrical force can drive metabolic activities and regulate specialized membrane proteins such as those regulating Ca^{2+}, Na^+ and K^+ fluxes [9, 15].

A fundamental principle for solutions with charged substances is the principle of electrical neutrality. It says that, in a macroscopic solution, the sum of all positive charges must equal the sum of all negative charges [16]. This means that once cells developed pumps and channels to regulate Na^+ concentration, the concentration of negative ions by necessity also were regulated to balance the charge. K^+ plays a similar role to Na^+ in maintaining the intracellular osmolality, but because K^+ is not directly connected to the outside of the organism, except for the small concentration of K^+ in plasma, it cannot directly regulate total body water. Accordingly, K^+ follows the concentration of Na, and by the same process, keeps intracellular osmolality the same as the extracellular space. For this reason, calculation of total body water deficits or excesses can be made just based on the concentration of serum Na^+ [17, 18]. The average intracellular K^+ concentration will reflect the Na^+ concentration.

Why Is the Concentration of Cl^- Less Than the Concentration of Na+?

Cl^- has the greatest mass of all elements in sea water and the concentrations of Na^+ and Cl^- are similar. So why did the serum concentrations of Cl^- evolve to a lower concentration than that of Na^+? First, there is the practical point that other negative charges need to be accounted for. There are two major ones in serum [19]. The first is bicarbonate (HCO_3^-), which is the dissociation product of carbon dioxide (CO_2), a major by-product of oxygen metabolism. HCO_3^- contributes about 22–26 mEq/L of negative charge at pH 7.4. A second component of negative charges comes from the dissociated proteins in blood. Albumin is the dominant one in plasma; it normally contributes between 16 and 17 mEq/L of charge. A second biological value of having a Cl^- concentration less than that of Na^+ is the effect on acid-base balance, which is discussed in the next section.

Strong Ions and the Concentration of Hydrogen Ion (H^+)

H^+ is unique among elements [20]. Because its core is only a single proton, it has the highest charge concentration of any atom. Its strong electrical field affects any molecules near it. Thus, a change in H^+ concentration can alter the tertiary structure of large proteins and nucleic acids well as the rates of chemical reactions. As a consequence, the concentration of H^+ is tightly regulated throughout the animal kingdom,

and the intracellular concentration of H^+ is similar from single celled organisms to humans [21]. Biological systems are water based and water molecules provide a large potential source of H^+. Release of freely active H^+ from water, as well as from weak acids, is strongly affected by the difference in the concentration of strong positive and negative ions. This is because the charge difference creates a strong electrical force that alters the dissociation of weaker molecules including water. In water based solutions, when the concentration of a strong negative ions, such as Cl^-, are greater than the concentration of strong positive ions, such as Na^+, the negative charge difference must be matched by altering the dissociation equilibrium balance of weaker ionic substances.

To understand the effect of strong electrolytes on water, it is first is necessary to define an acid solution in water. An acid solution is one in which H^+ is greater than OH^-; a neutral solution is one with $H^+ = OH^-$; and an alkaline solution is one with H^+ is less than OH^-. Almost all bodily solutions are alkaline by this definition.

In a solution with only Na^+ and Cl^- in water, the only substance that can dissociate to balance a charge difference between them is water, H_2O, which dissociates into H^+ and OH^-. When Cl^- is greater than Na^+ and extra negative charge must be balanced by H^+ [20, 22] (Fig. 13.1). Under this condition, narrowing of the difference in concentrations of Na^+ and Cl^- must be matched one-to-one with a change in H^+, and the solution becomes less acidic. When the reverse is true, and the concentration of Cl^- is less than the concentration of Na^+, the positive charge difference needs to be balanced by OH^- and the solution is alkaline. This is the situation in almost all bodily fluids [20]. A decrease in the concentration difference between Na^+ and Cl^- is matched primarily by a change in OH^- with a much smaller change in H^+. Thus, by having alkaline bodily solutions, changes in the concentration of strong ions in bodily solution have a smaller effect on H^+. This provides a stabilizing effect on cell structures that are impacted by changes in H^+ concentration.

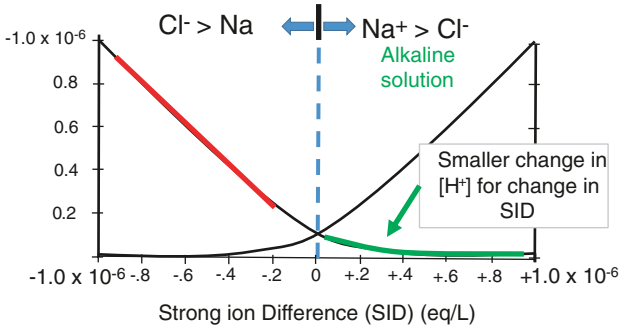

Fig. 13.1 Change in H^+ and OH^- with change in concentration of Na^+ relative to Cl^- (Strong Ion Difference). When the SID is negative, changes in Cl^- match changes in H^+ but when SID is positive changes in H^+ are much smaller than changes in Cl^- (or Na^+). The solution is also alkaline which is the case for almost all bodily solutions. To be able to display the changes on this figure the SID is presented only for differences of 1×10^{-6} (micromolar) whereas in plasma the difference in 40×10^{-3} (millimolar) and not seen on this scale

Based on the discussion above, the term balanced salt solutions refers to the impact of a solution on serum acid-base balance, which in turn is primarily determined by the difference between charges on strong ions. In plasma this requires that the concentration of Cl^- to be lower than that of Na^+ and creates an acid-base balance which actually is not neutral but alkaline. It is important to understand that the pH of an administered the solution is irrelevant for plasma pH because the plasma pH is determined by the final concentrations of all the ionic components.

Balance in the Body

Almost all discussions around potential benefits of balanced salt solutions revolve around the effect of these solutions on the composition of electrolytes in plasma because this is what can be sampled (Fig. 13.2). Furthermore, elements in plasma are in equilibrium with those in the interstitial space, except for minor deviations due the greater concentration of proteins in plasma than in the interstitial compartment, and what is called the Gibbs-Donnan equilibrium (Fig. 13.2) [10]. However, two thirds of body water is inside cells and the electrolyte composition of the intracellular compartment is very different from that of the plasma and interstitial space. Intracellular pH is in the range of 7.0–7.2 compared to 7.4 in plasma. K^+ is the dominant strong cation, Na^+ only is around 10 mmol, and Mg^{2+} is in the 20 mmol range (Fig. 13.2). The composition of negatively charged substances inside cells also is very different from the extracellular space. The difference between strong positive and strong negative ions (SID) is in the range of 130 mmol in contrast to 40 mmol in the plasma space. The intracellular Cl^- concentration normally only is in the 10–15 mmol range and regulated by a number of exchangers and channels [23]. The rest of the charge difference is balanced primarily by HCO_3^- and charges on amino acids, peptides and proteins. Red cells are an exception. Cl^- is 52 mEq/L and protein concentration is much lower than in other cells. Consequently the SID is around 57 mEq/L [20].

Physiological processes that evolved to regulate intracellular pH ultimately must involve shifts of Na^+, K^+, and Cl^- to regulate the difference in strong ions, but cells

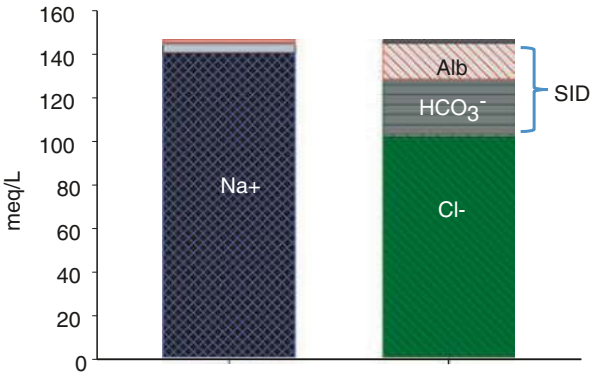

Fig. 13.2 Major electrolytes in normal plasma. The difference between strong positives primarily Na^+, and negatives, primarily Cl^- is the Strong Ion Difference and is primarily accounted for in plasma by the anionic form of albumin (Alb) and bicarbonate (HCO_3^-)

also create or metabolize substances that can balance the charge on strong cations. As with any physiological process, there are limits to these regulatory mechanisms and these limits cannot be easily predicted. They also likely vary among cell types. Empiric studies will be required to determine how infusion of Cl^- rich solutions alter the intracellular function and consequently organ function.

An important question that arises when investigating the impact of increased intake of Cl^- is whether it is Cl^- concentration that counts or the total amount of Cl^- in the body. H^+ concentration in each compartment, i.e. vascular space, interstitial space, or individual cells, is determined by the concentration of electrolytes in that compartment. Furthermore, H^+ concentration in each compartment only changes if the balance of strong ions changes movement into or out of the compartment, or inside cells by the production or breakdown of organic electrolytes, or by changes in total CO_2 content. It is possible that Cl^- can act on the outer-side of cell membranes [24] and trigger intracellular events, in which case the Cl^- concentration will matter. However, because Cl^- concentration inside cells normally is small relative to the plasma concentration, events inside cells could be affected more by the total amount of Cl^- in the body that diffuse into cells from the extracellular space [23, 25]. In that case, increased total body Cl^- could have effects on cell function even when the Cl^- concentration in plasma is normal. This would be the situation when there is massive edema. As examples, increasing the intracellular concentration of Cl^- in platelets increased epinephrine induced aggregation through the alpha-2 adrenergic receptor. Increasing intracellular concentration of Cl^- in vascular smooth muscle increases their contractility [26]. Lowering intracellular Cl^- concentration is required for tumor necrosis induced activation of beta-2 integrins [26].

How Is the Difference Between Na^+ and Cl^- in Blood Regulated?

As already indicated, the amount of an element in the body is determined by the amount taken in and the amount excreted because they cannot be metabolized. Direct infusion of salt solutions into blood is obviously very un-physiological for current organisms, although this was the case for early organisms in which fluids could move across cell membranes directly into cells from the surrounding milieu [11]. Our intake of Na^+ and Cl^- comes through the gastrointestinal tract, which has many mechanisms to selectively absorb electrolytes with a final ratio of Na^+ and Cl^- that is different from what is taken in by the mouth [27–30]. A good example is the stomach. The fasting state secretes a very acidic solution with Cl^- as the strong electrolyte. It often is not appreciated that although daily intake of water through the gastrointestinal tract is in the range of 2 L, the gastrointestinal itself secretes 8–10 L into the lumen, but almost all of it is reabsorbed. Through this process the gut can contribute to the regulation of electrolytes [31]. This regulatory mechanism likely is significantly reduced when patients are not fed.

Intake of solutions with ionic contents higher than normal body osmolality inevitably leads to dehydration and hypernatremia, unless there is intake of free water.

Attempting to drink a solution with high salt content, such as sea water, usually induces gaging or vomiting. There are a few reported cases of people ingesting large NaCl loads but these are not common. A fatal case of oral excess of Na^+ occurred in a man who was gargling with a concentrated solution of NaCl that contained between 1200 and 1500 mmol of Na^+ [32]. On presentation, his initial Na^+ was 209 mEq/L and it did not respond to infusions of hypotonic fluids. In another report, a young man drank about 1 L of soy sauce and drove his Na^+ to 196 mEq/L [33]. He survived with no neurological sequelae after receiving 6 L of free water over 30 min.

Avoidance of intake of large amounts of salt is even true in sea mammals, which have tissue osmolalities similar to land animals. Most get their water from eating their prey, which have tissue osmolalities similar to humans. They also get free water as a metabolic product. Some sea species, such as seals, supplement their free water with snow, but at times can take in small quantities of sea water. The major regulation of the balance of the body's elements and osmolality fall to the kidney, which is discussed next.

When functioning normally, this remarkable organ filters 180 L/day of plasma, 23,900 mEq Na^+, 19,742 mEq of Cl^- and other valuable constituents and then reabsorbs all but 1–2 L of the water, 99.6% of Na^+, and 99.5% of the Cl^- [11]. The small difference in the reabsorption of Na^+ compared to Cl^- creates the 40 mmol difference between Na^+ and Cl^- in plasma with likely some contribution by the gastrointestinal tract. The principle of electrical neutrality once again raises its head and creates a problem for renal excretion. To excrete more Cl^- than Na^+ an alternative strong cation is needed to balance excreted Cl^- in renal tubules. It also has be a cation that is only produced in the renal tubular cells, otherwise it would alter the concentration of H^+ in plasma. The evolutionary solution was the development of enzymes that produce ammonium/ammonia (NH_3/NH_4^+) by cleaving the nitrogen groups from amino acids [11, 34]. NH_3 itself has no charge so that it does not affect H^+ concentration. However, at body pH it readily binds H^+ to form NH_4^+ which acts as a strong cation.

The enzymes that produce NH_3 are decreased or even lost when there is renal tubular dysfunction [35] and the excretion of excess Cl^- is slowed even more than normal. Based on CaCl loading studies in human subjects with nephritis, initial Cl^- excretion largely involves excretion of excess K^+ which must be restored by increased intake of K^+ or else serum K^+ very rapidly becomes depleted and leads to death [11]. Some Na^+ also is excreted but this lead to significant volume depletion [36, 37]. These physiological arguments support my contention above that it is likely that the total body excess of Cl^- will be found to be more important than the concentration of Cl^- because the total amount of Cl^- stresses the renal tubular capacity to produce NH_4^+ and the need to use other essential positive electrolytes to excrete it.

As indicated above, the intracellular concentration of Cl^- normally is very low. However, to be excreted Cl^- must pass from blood through cells lining the gastrointestinal tract or from blood through renal tubular cells. Presumably these cells have evolved to handle these fluxes but one must wonder what are the limits of adaptation that allow excretion of high loads of Cl^- and to protect the intracellular H^+

concentration of these cells. Thus, the gastrointestinal tract and kidneys need be important organs to study when determining the potential toxicity of high Cl^- loads. Endothelial cells, vascular smooth muscle [26] and blood cells [26, 38] also could have abnormal function from high Cl^- loads.

Physiological Studies of Cl^- and Renal Function

High plasma Cl^- concentration has been shown to decrease renal blood flow and plasma clearance [23, 24, 39]. However, one must be cautious in interpreting these studies because the solutions used to increase the Cl^- load most often are very acidic and it is hard to know whether the change in function is due to the change in H^+ or the change in Cl^- itself. The proper experiment would require using a Cl^- salt with a strong cation that is not K^+ or Na^+ and not readily metabolized. NH_4Cl commonly is used in these studies but it actually increases plasma H^+ more than NaCl [39]. This likely is because the NH_3 can be cleared leaving unbalanced Cl^-. Furthermore, NH_3 diffuses freely into cells where it re-forms NH_4^+ and alkalinizes the intracellular environment. This can trigger counter responses inside cells and at the same time the decrease in NH_4^+ outside cells increases extracellular acidity. With these cautions in mind, animal studies on isolated vessels or whole kidneys provide some insights. A hypertonic solution of NaCl dilates all vascular beds. With the exception of the kidney, this is followed quickly by vasoconstriction [39]. The vasodilation in the kidney is not related to the concentration or clearance of Na^+, but is directly related to tubular Cl^-concentration. Both afferent and efferent arterioles are equally dilated because the fall in glomerular filtration rate (GFR) is proportional to the fall in renal plasma flow and fractional flow does not change. H^+ clearly plays a role for the effect is greater and fractional flow decreases more if NH_4Cl is used instead of NaCl. Prior volume depletion increased the response. Elegant studies on isolated afferent renal arterioles indicate that extracellular Cl^- modulates K^+ induced contractions through a Ca^{2+} dependent process, but in the study, approximately 30% of vessels did not respond [24]. Importantly, in these studies Cl^- had no effect on the ability of norepinephrine to constrict the vessels. Putting all these studies together, it becomes evident that the renal responses to high Cl^- load are dependent upon volume status, functional glomeruli that actually deliver Cl^- to tubules, and the presence of other vasoactive agents such as catecholamines.

Comparison of renal and whole body responses to 0.9% saline and the low Cl^- balanced salt solution, Plasma Lyte® 148, was studied in normal subjects who were not given fluid over-night [40]. The NaCl solution produced greater weight gain than the balanced solution. The difference in excreted volume was based on change in interstitial and not the plasma volume. As expected, serum Cl^- was higher, strong ion difference higher, and bicarbonate concentration lower in the NaCl group. Renal blood flow velocity and cortical blood flow also were lower in the NaCl group. This study in normal subjects clearly indicates a physiological differences in renal handling of these solutions, but does not indicate what the clinical significance would

be with differences in basal volume status, differences in renal function, decreased serum proteins, and in the presence of catecholamines, all of which modulate renal responses to Cl^- [40].

Balanced Salt and Gut Function

The large secretory function of the gut makes is very susceptible to large changes in the concentration of plasma Cl^- because a high load of Cl^- passing through the epithelial cells lining the gut will significantly acidify their cytoplasm, at least transiently. In the fasting state the stomach excretes a large amount of Cl^- but this largely is blocked by histamine-2 receptor antagonists and proton pump inhibitors, which are regularly used for gastric cytoprotection in critically ill patients. This process could still be important in perioperative patients. Intestinal jejunum secretes Cl^- but normally this process is overwhelmed by greater distal absorptive processes and these have to be blocked to identify Cl^- secretion [41]. Presumably jejunal cells are better designed to be protective on the luminal side for nature likely has not evolved to handle large Cl^- loads from the plasma side. Insight into the effect of Cl^- handling in the jejunum comes from persons with cystic fibrosis (CF) [42]. The classic defect in CF is abnormal secretion of Cl^- through the CF transmembrane conduction receptor (CFTR). This would be expected to reduce Cl^- in the lumen but the opposite happens. Absence of the CFTR greatly reduces movement of Cl^- out of the lumen through the tight junction para-cellular pathway. The Cl^- left in the lumen creates an osmotic load in the lumen that greatly decreases Na^+ and water absorption. This indicates that there is an interaction between receptors on luminal cells, luminal contents, and H^+ concentration that effect Cl^- handling by the intestine. On the other hand the diarrhea associated with cholera infections has been shown to be to uncontrolled efflux of Cl^- into the jujeunal lumen which creates an osmotic diuresis [43]. Because of their dysfunctional CFTR, people with cystic fibrosis are more immune to cholera potentially accounting for the high prevalence of this genetic defect [44]. It is hard to predict how these would interact after surgery when intestinal blood flow is potentially reduced, H^+ in the walls is likely higher because of the lactated solutions that are given intravenously [45] with greater Cl^- loads. This suggests that intestinal function should be a prime area of study on the potential benefits of balanced solutions in the perioperative period [46].

The effect of balanced salt solutions on intestinal function only has been examined in a few clinical studies that included a very limited numbers of patients. The studies also mixed patients receiving hydroxyethyl starch solutions with patients receiving just crystalloid solutions. Wilkes et al. studied 47 patients and found less vomiting, nausea and use of emetics in the group with a starch in a balanced salt solution [45]. A study by Moretti et al. is harder to interpret [47]. The population was again very small; three groups of 30 were given a hydroxyethyl starch dissolved in a balanced salt solution, the same starch dissolved in 0.9% saline or lactated Ringer's. Patients receiving the two colloid solutions had less nausea and vomiting than the lactated Ringer's group, but the two colloid groups also only required 1/4

to 1/3 of the volume of the lactated Ringer's group, which means that the Cl^- load was much lower.

What Substance Can Be Used to "Balance" Na^+ in Intravenous Solutions?

Under normal physiological conditions the charge on Na^+ is balanced by the weak acids from dissociated proteins (primarily albumin) [48, 49] and CO_2/HCO_3^- which has an effective pKa of 6.3. If CO_2/HCO_3^- were the only other element in a solution of pure water titrated with strong ions, a neutral solution (i.e. H^+ equal to OH^-) would occur at 6.3 when the strong ion difference is 50% of the concentration of the total CO_2 species [20]. The CO_2/HCO_3^- thus works by changing the neutral set point of the solution. Because CO_2 is volatile, the total content can be readily controlled through neuro-control of ventilation. CO_2/HCO_3^- commonly is used to reduce the Cl^- concentration relative to Na^+ in dialysis solutions, but it has not been used for standard intravenous fluids. This is because CO_2 is volatile and a much stiffer and more expensive plastic is required to keep the CO_2 from leaching out. CO_2/HCO_3^- also cannot be mixed with a solution that has Ca^{2+} or Mg^{2+} because it could precipitate out as a salt. An effective high HCO_3^- short term solution can be created by adding three ampoules of $NaHCO_3$ at 44 mEq/L of HCO_3^- into 5% dextrose in water. This gives a solution with 132 mEq/L of Na^+ and no strong anion.

Confusion often arises over the issue of giving or removing HCO_3^-. The variables that need to be considered when analyzing the effect of a weak acid on H^+ are the total amount of dissociated and non-dissociated species of the substance, the dissociation constant of the substance, and the charge on the anion of the substance. HCO_3^- is dissociated from the weak acid carbonic acid, which in turn is in equilibrium with CO_2 and its hydrated forms. The total amount of all these forms of CO_2 in a solution determines the concentration of H^+. Furthermore, the total amount of CO_2 and its products is regulated by metabolic production and clearance of CO_2 by ventilation, which is tightly controlled by the respiratory centres in the brain. Actual HCO_3^- concentration is dependent upon the contents of the solution. As an illustration of this point, HCO_3^- concentration normally is about 16 mEq/L inside most cells, 31 mEq/L in the interstitial fluid and 25 mEq/L in plasma [20, 22] which makes it look like HCO_3^- is moving up and then down its concentration gradient! What actually is happening is the other contents of the solution in each compartment alter the equilibrium of the dissociation of CO_2 species, but the total amount of CO_2 species decreases from the cell to plasma and eventually the lung. As long as ventilation can vary and maintain CO_2 constant, addition of CO_2 species only can transiently change HCO_3^-. However, this is not true when ventilation is totally controlled with mechanical ventilation. Thus, it is essential to know whether experiments assessing the effect of added HCO_3^- are done with controlled or spontaneous breathing. Although there is extensive discussion of bicarbonate secretion by the kidney [36], the concentration of HCO_3^- in renal tubular fluid is determined by the total CO_2 content, strong ion difference and presence of other secreted weak acids.

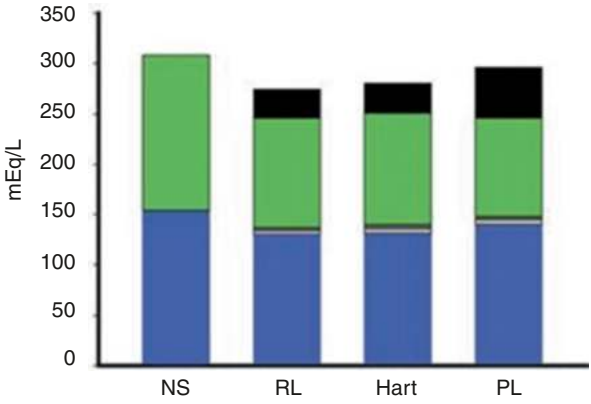

Fig. 13.3 Graphic composition of four commonly used intravenous solutions. *NS* normal saline, *RL* lactated Ringer, *Hart* Hartman's, *Pl* Plasma-Lyte-148. The peak of the bar indicates the osmolarity. The black region indicates anions added to compensate for Cl^-

The seemingly renal excreted HCO_3^- has little impact on total body CO_2 content. This is evident by the lack of increases in CO_2 in patients without kidneys. If anything total CO_2 goes down because of the metabolic acidosis increases ventilatory drive. CO_2 balance is primarily regulated by the lung. HCO_3^-, though, is determined by the strong ion difference and concentration of weak acids.

Commercial balanced salt solutions use the moderately strong organic acids lactate, acetate, and gluconate to replace Cl^- (Fig. 13.3). These all have pKa's in the range of 3–4 and thus are almost completely in dissociated forms in plasma and act as strong anions. It needs to be repeated that the pH of the infused solution does not determine the final pH of plasma for that is set by the final composition of the substances in blood. When first infused these strong anions are slightly acidifying because, as is the case with NaCl, they narrow the strong ion difference. However, they are quickly metabolized, primarily to CO_2 and water and have an alkalinizing effect because when metabolized, they leave behind Na^+ and widen the SID. In a spontaneously breathing person, with proper CO_2 regulation, total CO_2 does not change, but HCO_3^- concentration increases because the increase in the SID alters the dissociation of carbonic acid. The change in serum HCO_3^- depends upon how fast the organic anion is metabolized and the ventilatory response. This was nicely shown in calves with diarrhea [50]. Animals were infused with either a $NaHCO_3$ or gluconate based solutions. The rational was that gluconate is not readily metabolized, but rather excreted with Na^+. Thus, unlike the $NaHCO_3$ solution, there is no change in the SID and no alkalinisation of plasma, which is indeed what happened.

Lactate was one of the first organic ions to be used in what is called Hartman's solution as well as lactated Ringer's solution, both of which are still popular [4]. A concern is that the 28 mmol/L of lactate in the resuscitation fluid will raise plasma lactate and thereby makes it harder to use trends in lactate to guide fluid management. This is especially a concern in patients undergoing liver resection because it might make it difficult to detect liver failure. Pathological lactic acidosis is due to a combination of failure to normally metabolize glucose in mitochondria and failure to clear the lactate by the liver [51]. Thus, unless metabolism is deranged and liver function minimal, the amounts of lactate in the solution should have only modest

effects on plasma concentrations of lactate and a large increase in blood lactate should still indicate that there is a major pathological process [5, 52–54]. For example, in person with 12 L of extracellular, 1 L of lactated Ringer solution with a lactate concentration of 28 mEq/L, and no metabolism of the lactate, would raise the plasma concentration by 2.3 mEq/L. Importantly, lactate is used by muscles and the heart as a fuel [55]. If there is not a process that is pathologically increasing lactate or major liver failure, the relatively small the total lactate with infusions of lactated Ringer's solution should not have a large effect. Concern also has been raised that the K^+ in the solution could raise serum K^+ in patients with renal dysfunction, but the additional K^+ of 4 mEq/L is very small compared to the large concentrations in cells. Unless there is a water loss, K^+ will not rise above the 4 mEq/L in the solution [54, 56]. This was confirmed in a number of studies, which showed that. if anything, serum K^+ rose more with 0.9% saline [57, 58]. There is evidence in isolated kidneys that lactate increases K^+ excretion [59]. K^+ also fell when sodium lactate was infused in dogs without renal function indicating that this is likely due to intracellular shifts [60].

Acetate

Acetate is rapidly metabolized in blood and increases the concentrations of HCO_3^- more than lactate or succinate salts [48, 58, 60, 61]. Acetate in dialysate solutions are known to produce vasodilatation [62] and it was suggested that it also depresses cardiac function [63, 64] but in a study comparing acetate to HCO_3^--based dialysate acetate infusion actually increased cardiac function when assessed by echocardiography in humans [65] as well as in dogs [61]. In another study the effect of acetate on blood pressure was no different from that of a bicarbonate based solution [66].

Gluconate

Gluconate is not metabolized as efficiently as acetate and lactate in dogs, rats and calves. Consequently HCO_3^- does not increase as much. It is cleared largely by the kidney and seems to produce an osmotic diuresis [50, 60]. In the absence of renal function gluconate increased K^+ [61]. Concerns have been raised that gluconate can produce an inflammatory response, but the concentration of the major inflammatory cytokine interlukin 6 was not altered when gluconate was compared to bicarbonate based solution as a primer for the bypass circuit for cardiac surgery patients [67]. Of note, gluconate can result in a false positive galactomannan assay [68].

Other Anions

Succinate is commonly used as the anion for various drugs such as corticosteroids. In a study in dogs with no renal function, infusion of 0.25 mEq/kg/min produced similar changes in HCO_3^- as the same amount of lactate, but at a slightly lower rate

[60]. No hemodynamic toxicity was noted but K^+ rose as seen with gluconate. I found no studies in which succinate was used to balance Na^+ for resuscitation or maintenance fluids in humans. In dogs in which renal arteries were ligated, acetate, succinate and lactate salts increase serum bicarbonate [60]. There is a succinylated, gelantin product (Gelofusin®, B Braun Medical) but this should not be confused with a balance solution for the succinate just balances the gelatin. One product is dissolved in a solution with Na^+ of 154 mmol/L and Cl^- of 120 mmol/L and thus has a high chloride but a newer product is dissolved in a solution with a Cl^- of 105 mEq/L and 25 mmol/L lactate which is similar to lactated ringers (Isoplex®, IS Pharma).

Pyruvate is another anion that could balance Na^+ but it is toxic unless the enolate ethyl-pyruvate is formed [69]. This later substance has anti-inflammatory and oxygen radical scavenging properties and was being evaluated for intravenous fluids use [70]. However, it failed to show any benefit in a stage II trial in patients undergoing cardiopulmonary bypass [71]. In a second study on patients who had liver resections it acutely reduced inflammatory markers but then decreased hepatocytes regeneration when used as an alternative to n-acetylcysteine [72, 73].

Clinical Outcome Studies

Until recently there no properly designed randomized large clinical trials on the value of using balanced salt solutions for maintenance fluid management or resuscitation. The most recent update of the Cochrane analysis in 2017 found 18 randomized studies with a total of 1096 subjects and was done before the recent three large randomized trials. All the previous studies were hopelessly underpowered to make any conclusions, particularly on mortality benefits or harm. The collected publications included studies from subjects given balanced salt solutions as the solvent for colloid solutions and others that just used crystalloid solutions. A significant proportion of subjects were operated for kidney transplantation and thus a very specific population. The study periods with the tested solutions were short, and usually limited to the operative period and less than a day. After that use of 0.9% saline was uncontrolled and volumes infused were often many fold higher than the tested solutions. The only thing that can be said about the Cochrane report is that it indicates that there was no meaningful randomized clinical data before the recent three studies. Another Cochrane review has been planned for non-surgical patients [74] but as of the summer of 2019, only the protocol is published.

Observational Studies

Potential harm solutions with Cl^- concentrations higher than normal serum were supported by three large observational studies.

Shaw et al. analyzed a data set from almost a half million subjects who had undergone an open abdominal surgical procedure [75]. They excluded subjects who had received a fluid incompatible with use of citrate and were left with 30,994 subjects who had received 0.9% saline and 996 who received the balanced salt solution

Plasma-Lyte® (Baxter) on the day of surgery. There were some important baseline differences in the two groups. Patients receiving the balanced salt solution were more likely to have private insurance and be managed in large teaching hospitals which indicates differences in socio-economic class. To control for selection bias the authors developed a propensity score for use of a balanced salt solution and used it to match patients from the saline group with the Plasmalyte group. The saline group had more post-operative infections, a greater need for dialysis, more blood transfusions, more electrolyte abnormalities, more measurements of arterial blood gases, and more sampling of blood for lactate levels. Given the difference in baseline abnormalities, the question still exists whether the propensity score was able to adjust for baseline differences. Use of more blood tests was likely a real phenomenon because the higher Cl^- solution produces a negative base excess which likely triggered unnecessary blood tests by those naïve to the concept. The increased infection rate remains an interesting question that is worth pursuing considering the evidence that a high Cl^- concentration reduces activation of beta-2 integrins in neutrophils [38] which could reduce their antimicrobial actions.

Yunos et al. performed a sequential period pilot study at a single center with a little over 750 patients per period [76]. In the first 6 month period the hospital used the standard intravenous solution at that time which was primarily a Cl^- rich solution. The next 6 months was a wash out period in which Cl^- rich solutions were restricted and the fluids used were Plasma-Lyte 148, a lactated solution (Hartman's) or Cl^- poor 20% albumin, unless there was special request by a physician. In the third period use of diminished Cl^- solutions was continued. The mean Cl^- infused decreased from 694 to 496 mmol/patient, which is the equivalent of the Cl^- in 2 L of normal saline. The intervention resulted in less renal injury, less renal failure and less renal replacement therapy. There was no effect on mortality, hospital stay or need for renal replacement after hospital discharge. In summary, this study demonstrated increased acute renal injury but no lasting renal effects. The total difference in Cl^- given was not large which could be considered a weakness or on the other hand be important because an effect on renal function was observed. Limits of the study are that clinicians knew that there was a change in standard practice, serum levels of Cl^- were not reported and there were no pre-defined criteria for renal replacement therapy, which could have been partially driven by the observation of Cl^- induced metabolic acidosis, but not necessarily clinically indicated.

McCluskey et al. determined the incidence of hyperchloremia defined as Cl^- concentration >110 mmol/L in a data set of 22,851 patients who had undergone non-cardiac surgery and whether the hyperchloremia was associated with length of hospital stay, morbidity or 30 day mortality [77]. Hyperchloremia was common; it occurred in 22% of subjects and was associated with a higher mortality (3.3% vs. 1.4%), longer length of stay and more renal injury. As in any retrospective analysis it always is possible that the increased Cl^- concentration was just a marker of patients at risk. To further analyse this possibility, these authors, too, performed a propensity analysis. Risks for developing hyperchloremia included sex, emergent surgery, last pre-operative hemoglobin, main service of the operative procedure, procedure time, and minimum hemoglobin on post-operative day 1. Patients at risk

for hyperchloremia were indeed sicker than those without but despite this increased risk there were more deaths, a longer length of hospital stay and a greater incidence of renal risk in those who actually developed hyperchloremia than those who did not. Since this was not a controlled intervention trial, the higher incidence of events could still be because of some other uncontrolled factors, and in particular, diabetes.

Randomized Trials

SPLIT Study

SPLIT was the first large randomized study to compare 0.9% saline to a balanced salt solution [78] although the authors still considered it a pilot study because it was not powered for mortality. A larger study is underway. In SPLIT, 2278 patients were enrolled in a double-blind cluster randomized cross-over design in four hospitals. Each hospital used the assigned fluids for 7 week periods twice during the study. There was no protocol for the use of fluids. The primary end-point was a doubling of serum creatinine or a serum creatinine level greater than 3.96 mg/dL with an increase of ≥0.5 mg/dL from baseline. There were no differences in the primary end-points or use of renal replacement therapy between the two groups. If anything the relative risk of death favoured the saline group (saline 7.6% and balanced salt solution 8.6%). This study would seem to indicate that balanced salt solutions provide no benefit. However, the study has many limitations which were very well covered in the excellent accompanying editorial by Kellum and Shaw [2]. The most important relate back to issues that I have already raised in discussion of the potential pathophysiology of excess Cl^-. In particular, the study did not provide information that could help determine whether the serum concentration of Cl^- or total amount in the body that is key; the concentration of Cl^- was not even reported. Another important factor is that the average volume given only was 2 L and it was given in 24 h. Thus, the total load of Cl^- given was not high and much lower than in the Yunos et al. [76]. There was no stratification of subjects at high risk for hyperchloremia as identified by McClusky et al. [77]. The percent of patients with comorbidities also was low and the percent with diabetes was not reported. Baseline creatinine values were in the normal range and similar in both groups. In summary, this was a relatively low risk populaton who received a moderate amount of fluid. What can be concluded is that moderate use of saline solutions in low risk subjects have at most small effects on renal function and no effect on mortality. The potential effect on bowel function in post-operative patients and infection rates were not assessed. The study gives no indication of potential effects in higher risk patients.

SALT Studies

Since the first addition of this book, the SALT investigators have published two studies on balanced salt solutions [79]. SALT-ED was a single-centre, pragmatic,

multiple-cross-over trial that compared use of balanced crystalloid solutions with 0.9% saline for fluid management in adults who required intravenous crystalloids in the emergency department, and who were subsequently hospitalized outside the intensive care unit [80]. The balanced salt solutions in this study were lactated Ringer's solution or Plasma-Lyte A®. Random assignment of solutions were altered every month for all units in the study hospitals. A total of 13,347 adults were enrolled over 16 months. The primary outcome was hospital free days before day 28; the median of 25 days was identical in both groups. This also indicates that most patients had a very short stay. A secondary end-point was a composite of major adverse kidney events within 30 days. The incidence of 4.7% in the balanced salt group was slight lower than the 5.6% in the saline group. However, a closer look at the term is useful. Major adverse kidney events were a composite of death, new renal replacement therapy, or a persistent increase in serum creatinine, or ≥200% at hospital discharge or 30 days. The 3689 patients who received less than 500 mL were excluded from this analysis meaning that this is a modified intention to treat. Cl^- rose in both groups but more in the saline group. It is worth noting that serum Cl^- was >110 mmol/L in over 15% of the balanced group. By 72 h the values were very similar. An important limitation of the trial design is that there was no stratification by risk. As in any study an advantage to a treatment could come from a benefit or failure to treat those in need in the control group. Indeed, this concern was raised by De Backer and Vincent when the study protocol was published [81]. It is worthwhile digging down further into the results. The composite major adverse kidney event within 30 days was 315 vs. 370, a difference of 55 patients, renal replacement therapy was 18 vs. 31, a difference of 13 and a creatinine increase of >200% was 253 vs. 293, a difference of 40, all in favour of the balanced salt group. The mortality was 94 in the balanced group versus 102 in the saline group, a difference of 8. It is worth remembering that this is out of 13,447 participants, and thus very low rates. Importantly, this study was not blinded and it is possible that increased renal replacement and even deaths could have been due to over-zealous and unnecessary treatment.

In SMART the same protocol was applied to patients who were admitted to intensive care units [82]. This study included 15,802 adults. The primary outcome was not hospital stay but rather the major adverse renal outcome criteria that was a secondary outcome in SALT-ED. This occurred in 14.3% (1139) of the balanced group versus 15.4% (1211) of the saline group, a difference of only 72 subjects, but it gave a statistically significant odds ratio of 0.84–0.99 in favour of the balanced group in this very large sample size. There was no significant difference in death rates which was 10.3% in the balanced group and 11.1% in the control group, nor was there a significant difference in the incidence of new renal replacement therapy.

SMART has been lauded by some as finally providing proof of the advantage of a balanced salt solution over saline, but I believe that it fails to do so. My criticisms of SALT-ED apply to SMART. However, the more major problem could be more subtle and goes back to the criticism of de Backer and Vincent [81]. Based on the study design only saline was used for during the saline periods. This

indicates that normal saline must have been used for maintenance fluids instead of half normal saline. If saline was given at a rate of 100 mL/h patients it have received almost four times the recommended daily intake of Na^+ and a great excess use of Cl^-. What the SALT studies have shown is that a higher Cl^- concentration is associated with worse renal outcomes and that monitoring serum Cl^- concentration needs to be an essential component of fluid management. Composition of infused fluids needs to be changed when Cl^- concentration is elevated. It likely is especially important in high risk groups, such as diabetics or chronically hypertensive patients.

PLUS

Another multi-centre, blinded, randomised, controlled trial called PLUS is underway. It will compare fluid resuscitation with Plasma-Lyte 148® in a total of 8800 patients (ClinicalTrials.gov Identifier: NCT02721654). The primary end-point is 90 day mortality. I would expect that the outcome likely will be very similar to the SALT and SPLIT because it suffers from the same design problems in that it overuses saline in the control group and fails to stratify by high risk groups.

Design of Studies

What can be learned from the studies to date? The three large observational studies suggest there is a signal for increased risks of injury with use of Cl^- rich solutions, but as is the case for all observational studies, they contain biases which make it hard to determine if the negative outcomes in the Cl^- rich groups are just an association or caused by increased Cl^-. In SPLIT [78] and SALT-ED [79] it seems clear that use of Cl^- rich solutions in moderate amounts in low risk patients is not harmful. What has not been addressed to date is whether use of a large volume of Cl^- rich solutions causes harm and whether higher risk groups with less ability to clear Cl^- are more susceptible to adverse outcomes with high Cl^- solutions. The important question of bowel function after surgery has not been adequately addressed in any study. The increased risk of post-operative infections observed in the study by Shaw et al. [75] should also be included in future randomized studies. I see little value in answering these question with data-base studies for they lack the potential of tracking Cl^- concentrations in patients, the amounts of fluid given and the potential of identifying important clinical measures. Future studies will need to be in targeted subjects and with targeted endpoints such as post-operative bowel function, infection rates, and renal function and will require sample sizes likely in the 5000–10,000 range. Death as an endpoint would likely require an even larger sample size but will make it difficult collect a rich enough clinical data set. Perhaps a group that could be studied with a smaller sample size is those who are expected to have a longer stay in the ICU and likely will be exposed to a higher load of Cl^-.

Clinical Considerations in the Peri-operative Period

The physiological rational for controlling the amount of infused Cl^- is strong and the observational studies show a relationship of use of higher Cl^- solutions and effects on kidney function, infections and possibly even mortality. However, the randomized studies that have addressed causation showed little or no benefit. On the other hand failure to demonstrate a lack of benefit does not mean that there is no benefit. When there is a potential benefit from a treatment but lack of evidence, cost and safety become important factors. It appears that lower Cl^- solutions are safe and the available products are not much more expensive than normal saline. While we await proper studies clinicians might want to consider using these products in higher risk populations. I would recommend broadening the identification of this group from the criteria used by McCluskey et al. [77]. Based on my physiological analysis of the actions of Cl^-, renal tubular function may be more important than glomerular filtration, although they likely are related. Diabetics and patients who have recently received intravenous contrast might be at higher risk, too. Animal studies suggest that volume status and use of catecholamines modify responses to Cl^- [39]. Patients who are expected to receive large amounts of fluid are likely at higher risk because of the larger total load of Cl^- and in surgical cases this can be predicted by the type of surgery, whether the surgery is done as an emergency, the risk of hypotension, and the expected length of surgery as was done by McCluskey et al. [77]. Finally, any study examining the role of Cl^- need take into account the observation of Shaw et al. [75] that more tests were performed in subjects given solutions with higher Cl^- likely because clinicians were reacting to the acidemia produced by hyperchloremia and not appreciating the benign cause.

Conclusion

Elevated Cl^- concentrations in the body is an un-physiological condition. The potential significance is elevation of H^+ concentration with consequent effects on functions of multiple proteins. The evidence to date suggests that moderate amounts of Cl^- can be handled by the body, but the effect of large amounts of Cl^- rich solutions in higher risk subjects is unknown. It needs to be determined whether the important variable is the concentration of Cl^- or the amount of Cl^- in the body. Likely both are important but have different consequences. What is evident from the observational studies is that the metabolic derangements produced by Cl^- rich solutions can trigger unnecessary laboratory testing and clinical interventions when the cause is not appreciated. Given the very high use of crystalloid solutions, the clinical impact of Cl^- rich solutions still needs to be resolved in proper large randomized, targeted studies that are not pragmatic but include protocols that regulate total volume given as well as the type of fluid given. They also must address specific end-points of processes that can be affected by increased Cl^- which include bowel and kidney function, immunity, coagulopathy, red cell survival, and response to catecholamines.

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Positive Fluid Balance and Patients' Outcomes

14

John Danziger

Abstract

A large percentage of hospitalized patients are readmitted within 90 days of discharge with heart failure. Emerging observational data suggest that positive fluid balance that occurs during the hospitalization, particularly among patients at risk for fluid retention, is associated with poor outcomes. Consequently, careful and judicious attention to both fluid administration and to overall fluid balance during the hospital stay is important. To this end, understanding the physiology of the distribution of body fluid compartments, and that both the arterial and the venous aspects of the vascular space are independently important, is critical to patient care. In this chapter, we will review the clinical data outlining the potential risk of positive fluid balance and the physiological mechanisms that might influence the physician's decision whether to administer intravenous fluid or diuretics. Ultimately, despite a large amount of data highlighting the potential risks of excess fluid during a hospital stay, well-designed trials that use diuretics to reestablish euvolemia upon discharge are needed to further guide management.

Key Points

1. Heart failure is a common cause of rehospitalization.
2. Positive fluid balance during a hospital stay is associated with an increased risk of post hospitalization mortality.

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3. Given that many patients do not spontaneously diurese administered fluid, judicious use of intravenous fluid and close monitoring of fluid balance are critical.
4. Understanding the physiology of the distribution of body fluid is important to patient outcomes.
5. Given that the barrier between the vascular and interstitial compartments is permeable to sodium and water, intravenous isotonic fluid distributes into both compartments.
6. The body cannot accurately determine its own fluid volume status, but, instead, relies on surrogate markers to determine "sensed volume."
7. Whether restoration of euvolemia prior to discharge will lead to improved patient outcomes will require further study.

Introduction

A landmark *New England Journal of Medicine* study suggests that about one-third of Medicare patients are rehospitalized within 90 days of discharge [1]. The most common reason for rehospitalization is heart failure, followed by pneumonia. Although pneumonia perhaps might be expected due to a variety of posthospitalization conditions, including patient deconditioning, aspiration, pulmonary atelectasis, or previous institutional exposure, the explanation for why almost 10% of medical patients are rehospitalized due to heart failure is harder to understand. It is plausible that postdischarge cardiac events might occur. Or perhaps, upon discharge home with more palatable foods than typical hospital fare, patients forgo dietary sodium restriction. Perhaps, diuretic noncompliance contributes too.

However, it is also possible that the fluid retention that occurs during a hospitalization might have a pathogenic role. There remains a paucity of data or rigorous studies on the importance of fluid balance during hospitalization. In fact, data suggest that fluid balance is not even being carefully followed. In a recent critical care study, only 50% of patients in an intensive care unit (ICU), the highest level of patient care, had the admission and discharge weights recorded [2]. On the general medicine wards, dietary sodium restriction is prescribed widely, yet so too is the administration of saline fluid, often in ubiquitous and unrecorded ways, including maintenance fluids, "to keep open" intravenous lines, electrolyte repletion, and in various medications. As context, each liter of saline has 9 g of salt (approximately 3 g of sodium and 6 g of chloride). Given that the recommended low-sodium diet is 2 g of sodium, it is always perplexing to see a patient on a low-sodium diet receiving saline fluid.

Fluid administration is clearly important and a mainstay of therapy for a wide range of illnesses. This chapter does not argue against the judicious use of fluid as directed by the clinician. But instead, it attempts to focus on the importance of fluid balance as an independent predictor of outcomes. We will begin with a review of the clinical data linking fluid balance to patient outcomes and then delve into the pathophysiological explanations that support these clinical observations.

Fluid Balance and Outcomes: Summary of Clinical Studies

No textbook chapter can replace sound bedside clinical decision-making about fluid administration. And clearly, particularly, in the intensive care unit, indications for fluid administration are myriad, complex, and ultimately require careful consideration of the risks and benefits. The potential benefits are well known, and include improved hemodynamics, organ perfusion, and, potentially, outcomes. As has been clearly elucidated in a wide range of acute illnesses, including septic shock, postoperative redistributive shock, and burns, aggressive and timely fluid administration is essential. In 1991, a landmark study by Rivers et al. outlined the benefits of early fluid resuscitation for the treatment of severe sepsis [3]; 260 patients admitted with severe sepsis were randomized to early goal-directed therapy (EGDT) or standard therapy. EGDT consisted of a 500-ml bolus of crystalloid every 30 min to achieve a central venous pressure (CVP) of 8–12 mmHg. Of the EDGT group, 30.5% died within the hospital, compared to 46.5% in the standard therapy group ($p = 0.009$). Consequently, EGDT has become a standard of practice in critical care. However, there are several important caveats of that study that should be appreciated. Pulmonary edema was an exclusion criterion, and only 30% had a history of congestive heart failure. Furthermore, the total amount of fluid administered to both groups was essentially the same (approximately 13 l at 72 h). Thus, the Rivers study is primarily one of fluid timing, not amount. It concludes that early administration of fluid is beneficial to septic patients with low CVPs who typically have positive blood cultures, as would be expected with those with "leaky" capillary physiology. But it does not address the question of fluid balance. In the time period after resuscitation, several days after the operation, or once the blood cultures have become negative and the fevers resolved, do patients still need fluid? And what are the potential sequelae of this fluid once it is administered? Ultimately, the less understood question is what happens to administered fluid after the patient is stabilized, and how to approach the longitudinal management of fluid balance.

Recent data have focused on the importance of fluid balance during critical illness. In a recent meta-analysis of almost 20,000 ICU patients, restrictive fluid management was associated with a 60% lower risk of mortality compared to liberal fluid management. A wide range of studies, including many smaller observational studies, many of which lacked discrete outcomes, limits the full interpretability of this conclusion, yet does raise awareness for fluid judiciousness, particularly in sepsis. In the Vasopressin in Septic Shock Trial (VASST), a more positive fluid balance at day 4 was associated with increased mortality [4]. In a smaller prospective observational study of 42 patients with septic shock, a positive fluid balance at 48, 72, and 96 h was associated with increased mortality, despite similar characteristics of the groups upon admission [5]. In a prospective study that examined the association of daily fluid balance for 7 days after sepsis onset, nonsurvivors had significantly greater daily positive fluid balance than survivors [6]; and a small study suggests that achieving negative fluid balance is associated with improved survival [7]. Several trials have suggested that fluid restrictive management of mechanically

ventilated patients leads to shorter mechanical ventilation and less oxygen requirements [8, 9]. Much of this data, however, is observational, and the results should be interpreted with great caution. It is likely that significant confounding due to indication limits the interpretability of these findings, since sick patients, who are more likely to die, are probably more likely to also receive fluid. A well-designed study that randomizes resuscitated septic patients to standard care versus diuretics is needed.

The association of positive fluid balance with poor outcomes has also been extended to other patient populations [10–14]. The Program to Improve Care in Acute Renal Disease (PICARD) study group illustrated that fluid overload was associated with higher mortality in patients with kidney disease [15]. In 144 acute care surgery patients, those that achieved a negative fluid balance at postoperative day 5 had a 70% increased survival benefit [16]. Positive fluid balance has been associated with increased length of stay in coronary artery bypass grafting (CABG) patients [17] and increased mortality in noncardiac surgical patients [18]. In a small pediatric study, postoperative positive fluid balance was associated with hypertension [19].

In the largest study to date, inclusive of almost 16,000 medical and surgical ICU survivors, the association of fluid balance at ICU discharge with 90-day mortality was examined [2]. Compared to patients in the lowest fluid balance quartile (median [IQR], 1.5 [3.1, 0.7] L), those in the highest quartile (7.6 [5.7, 10.8] L) had a 35% higher risk of 90-day mortality in adjusted analysis. However, importantly, this association was not observed in all patients. In those without a history of heart failure or kidney disease, fluid balance at discharge was not associated with subsequent mortality, whereas, in those with a history of heart failure, history of acute kidney injury (AKI), or impaired renal function at ICU discharge, the association of positive fluid balance with increased risk of death was strengthened. This might suggest that in patients without fluid-retentive tendencies, administered fluid is eventually diuresed, whereas in those with cardiac or renal disease, spontaneous diuresis does not occur, and administered fluid might lead to chronic volume expansion.

A potential negative effect of fluid excess has been documented in nonhospitalized settings too, particularly in the care of patients with cardiac and renal disease. Increased body fluid, as measured by either jugular venous pressure [20] or radiolabeling techniques [21], is associated with increased mortality in heart failure. In patients with end-stage renal disease, fluid accumulation has been associated with a range of adverse effects, including hypertension, heart failure, left ventricular hypertrophy, and mortality [22, 23]. Similarly, a recent study of ambulatory patients with mild-to-moderate chronic kidney disease suggested that overhydration, as measured by bioimpedance, had an increased risk of cardiovascular mortality during 2 years of follow-up [24].

Despite a significant amount of observational data linking fluid excess with poor outcomes, the question as to whether the fluid per se, or the underlying pathophysiology that leads to the fluid retention in the first place, remains central. Without a well-designed clinical study that aims to specifically study the effect of reducing fluid excess, this question will go unanswered.

Why Is Fluid Given and Where Does It Go?: The Body Fluid Compartments

Given the competing tug between achieving adequate fluid resuscitation, clearly important in the care of critically ill patients, and the potential longitudinal harm of excess fluid, a review of the physiology of fluid hemodynamics, with a particular focus on the distribution of fluids and the internal mechanisms of sensing fluid balance, is provided as follows.

The Body Fluid Compartments

Body fluid, which is primarily made of up sodium, chloride, and water, comprises about two-thirds of body weight, the remainder consisting of solid tissue (primarily bone). The three major fluid compartments are the intracellular, intravascular, and interstitial spaces (Fig. 14.1). The cell membrane separates the intracellular space,

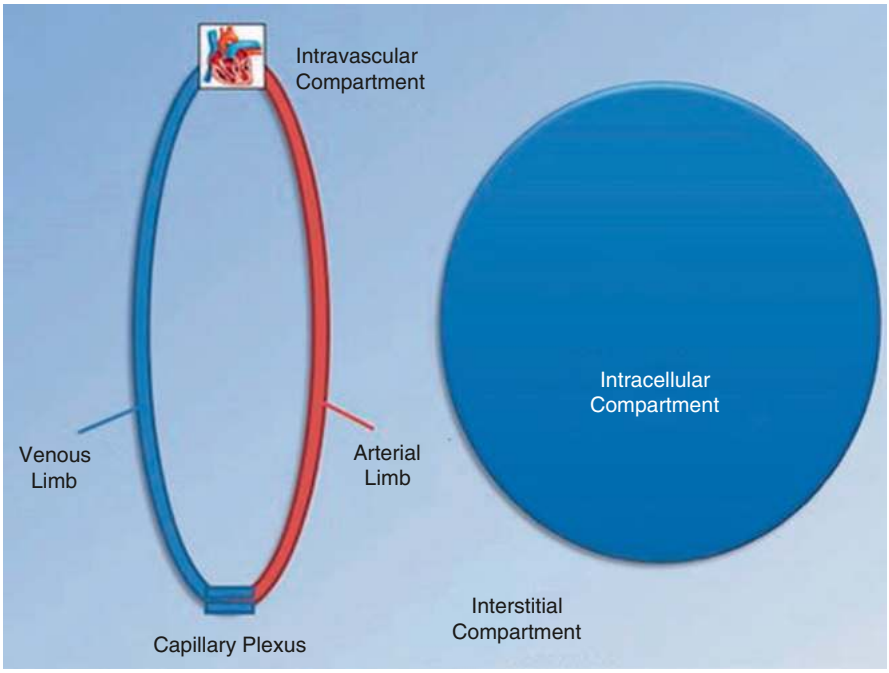

Fig. 14.1 Although the distribution of body fluid has traditionally been divided into three compartments, namely, the intravascular, interstitial, and intracellular compartments, this somewhat oversimplified approach fails to reflect the complex physiology of fluid hemodynamics. First, the capillary wall is freely permeable to sodium and water, and therefore, isotonic fluid moves freely between the vascular and interstitial compartments. The cell membrane is essentially impermeable to isotonic fluid, given Na/K ATPases embedded within the cell membrane. Thus, when considering fluid balance, there are primarily two definable compartments: intracellular and extracellular. Furthermore, within the intravascular compartment, there are two distinct limbs, the arterial and the venous, both of which are independently associated with clinical outcomes

and as a biological membrane with active Na/K ATPases, is permeable to water, but functionally impermeable to sodium and chloride. Thus, changes in water balance, as may occur in the setting of hyponatremia and hypernatremia, lead to alterations in cell size, whereas changes in isotonic fluid balance, as occurs in disorders of sodium regulation—such as heart failure, sepsis, or liver disease—affect the extracellular compartment (EC) only. In other words, a liter of retained water will primarily distribute into the intracellular space (666 ml in the cell, 220 ml in the interstitium, and 110 ml in the intravascular space), whereas a liter of retained isotonic fluid will remain exclusively in the extracellular compartment, with 333 ml in the intravascular space and 666 ml in the interstitium.

Measurement of body fluid volume primarily refers to changes in the size of the extracellular compartment, since even small changes in the size of intracellular compartment can have disastrous consequences. Retention of several liters of water, which manifests as hyponatremia, causes brain swelling, and, given the space limitations of the calverium, can lead to increased intracranial pressure and a range of neurological problems, including headaches, altered cognition, seizures, and death. Consequently, our body has developed a tight regulatory system to deal with potential alterations of cell size due to water imbalance [25]. Embedded deep within the brain, the osmoreceptor is a modified neuron with stretch receptors within its cell membrane. During times of cell swelling, as occurs with water excess, these receptors deactivate the osmoreceptor, which in turn downregulates vasopressin release from the posterior pituitary and extinguishes thirst. During times of cell shrinkage, as occurs with water deficit, the reverse happens, and the osmoreceptor stimulates vasopressin release and thirst. Vasopressin travels to the renal collecting duct, and after binding to its receptor, stimulates the trafficking of water channels into the collecting duct apical membrane, stimulating water reclamation from the duct back into the body. Unlike water retention, however, retention of isotonic fluid is mostly asymptomatic. A large amount of fluid can accumulate in the extracellular space without immediate consequences. Furthermore, unlike the tight regulation of cell size, the body lacks the ability to accurately detect the size of the extracellular compartment.

Previously, given that the intravascular volume perfuses vital organs, attempting to characterize the amount of fluid within the intravascular compartment, particularly the arterial compartment, has received much focus. Concepts such as "intravascular volume" or "effective arterial volume" attempted to describe the amount of circulating arterial volume that perfused organs. Early experimental studies used dilution technique to estimate body compartment volumes, whereby a known amount of radiolabeled tracer would be injected, and its dilution according to time would be used to estimate the intravascular compartment volume. Tracers such as Evan's blue, which binds avidly to albumin, or radio-iodine labeled serum albumin (RISA) were used. Intravascular volume was measured with radio-chromium labeled red cells, but is limited by in vivo differences in the hematocrit within different parts of the circulation, particularly differing between large and small vessels.

However, emerging evidence, as reviewed later, suggests that these terms, though conceptually pleasing, are physiologically inaccurate. Data suggest that some of the

traditional mechanistic explanations used to support the concept of a distinct and definable "intravascular" volume need to be updated. First, Starling's law, which suggests that fluid movement across a semipermeable membrane is simply governed by the algebraic sum of outward hydrostatic and inward oncotic pressure, is likely an oversimplification. The traditional molecular model of the capillary wall was simply a fenestrated, permeable barrier between interdigitating endothelial cells in dog hind limbs [26]. Intravascular volume was thought primarily to be due to a balance of venous pressure and plasma protein concentration [27]. However, in the 1960s, an increasing awareness of a "matrix of molecular fibers" that covers the endothelial lining emerged [28], and subsequently, the role of the endothelial glycocalyx as a determinant of transcapillary fluid movement has challenged the Starling model [29]. More modern data suggest that the inward oncotic forces are much less significant than originally thought, and that the filtered fluid likely does not return to postcapillary venules, but rather is absorbed by the lymphatic system [30, 31]. The endothelial glycocalyx contributes to the overall permeability of the capillary wall, and given its fragile and complex structure, is disrupted by a range of acute illnesses. Accordingly, albumin infusions, once widely accepted in resuscitation, have more recently fallen out of favor compared to isotonic crystalloids [32], despite previous supportive data [33]. A more updated fluid paradigm minimizes the inward oncotic pressures, and instead focuses on capillary permeability and outward hydrostatic pressure [34, 35].

Understanding hydrostatic pressure within the vessel well is no easy task. There remains no gold standard to accurately define the ideal vascular hydrostatic pressure. As seen in Fig. 14.1, there is an arterial limb and a venous limb, joined by a capillary plexus. Furthermore, within several organs, including the portal system and the kidney, there are additional capillary beds placed "in series" that further complicate the idea of a singular vascular volume, and the relationship between volume and pressure within these beds is complex. Mean arterial pressure, which reflects volume within the arterial limb, is affected by a host of regulatory mechanisms, including vascular tone, the sympathetic nervous system, and the renin-angiotensin-aldosterone system (RAAS). Central venous pressures are typically used to estimate filling of the venous system, but are affected by other factors, particularly right-sided cardiac function.

In addition to the complexity in choosing which vascular bed to measure hydrostatic pressure, perhaps the greatest challenge in interpreting hydrostatic pressure is due to the permeability of vascular wall, specifically the capillary endothelium. Given that the capillary is freely permeable to water and electrolytes, fluid can move freely and dynamically across the capillary. Administered isotonic fluid rapidly leaves the intravascular space for the interstitial space, ranging from 60 to 110 ml/min for normal volunteers, although somewhat less in ill patients [36]. Even in patients with relative "intravascular hypotension," as after major cardiac surgery, patients frequently may have high amounts of extravascular lung water [37], presumably due to increased pulmonary capillary permeability [38]. Thus, whereas volume resuscitation improves arterial hydrostatic pressure in certain conditions, such fluid eventually leaks into the interstitial space, and gradually reaches

equilibrium within the venous and arterial limbs. Thus, conceptually separating the intravascular compartment from the interstitial compartment is a physiological oversimplification. Ultimately, when considering isotonic fluid there are only two body compartments: the intracellular and the extracellular spaces. The blood vessel wall, which separates the vascular and interstitial compartments, is permeable to sodium and water, and there is constant and dynamic flow between the blood vessel and interstitial space. When considering fluid management, the intravascular and interstitial spaces should be considered as a single compartment.

In addition, using renal function—including both renal sodium handling (i.e., urinary sodium or fractional excretion of sodium), renal filtration (i.e., change of creatinine), and urine formation—as indicators of intravascular volume status is fraught with error and physiologically incorrect. Because activation of the renin-angiotensin-aldosterone (RAAS) system is activated by true volume depletion, as occurs with vomiting and hemorrhage, and by true volume overload, as occurs with heart failure or renal artery stenosis, urinary sodium is useless in determining volume status. Urinary sodium and renal function rather reflect "sensed volume," a term that underscores how the body responds to its own perception of its fluid volume status, and will be reviewed in the following section.

Internal Sensing of Fluid Balance

As seen in Fig. 14.2, there are two primary surrogate detectors of extracellular fluid, namely, the baroreceptors within the cardiac ventricle and the carotid vessels, and the juxtaglomerular apparatus (JGA) in the renal tubule. Neither of these sensors actually detects extracellular fluid volume.

Baroreceptors are stretch-sensitive fibers located primarily in the aortic arch and the carotid sinuses, near the common carotid artery bifurcation, and detect pressure. Afferent fibers from the carotid sinus baroreceptors connect to the medulla via the glossopharyngeal nerve, whereas extracarotid and cardiac baroreceptors connect to the brain stem via the vagus nerve. Collectively, these stretch receptors have an efferent limb that controls the balance between the sympathetic and parasympathetic systems, in turn, regulating cardiac function, vascular smooth muscle cell contraction, and renal natriuresis. In addition, direct stretch of the cardiac chambers can cause the release of natriuretic peptides that regulate renal sodium handling.

Likewise, the juxtaglomerular apparatus does not detect volume, but rather, tubular flow. It consists of three components: the macula densa, the extraglomerular mesangium, and a vascular element that involves the terminal parts of the afferent arteriole containing renin-producing juxtaglomerular cells. The macula densa is made of a group of 20–30 modified epithelial cells in the thick ascending limb of the renal tubule. Using a $Na^+2Cl - K^+$ co-transporter (NKCC2), these cells detect tubular flow. Although actually measuring chloride concentration, since the predominant determinant of chloride delivery is tubular flow, the macula sense can be thought of as measuring renal tubular flow. In turn, tubular flow is primarily determined by the glomerular filtration rate and proximal sodium reclamation. Thus, in settings of

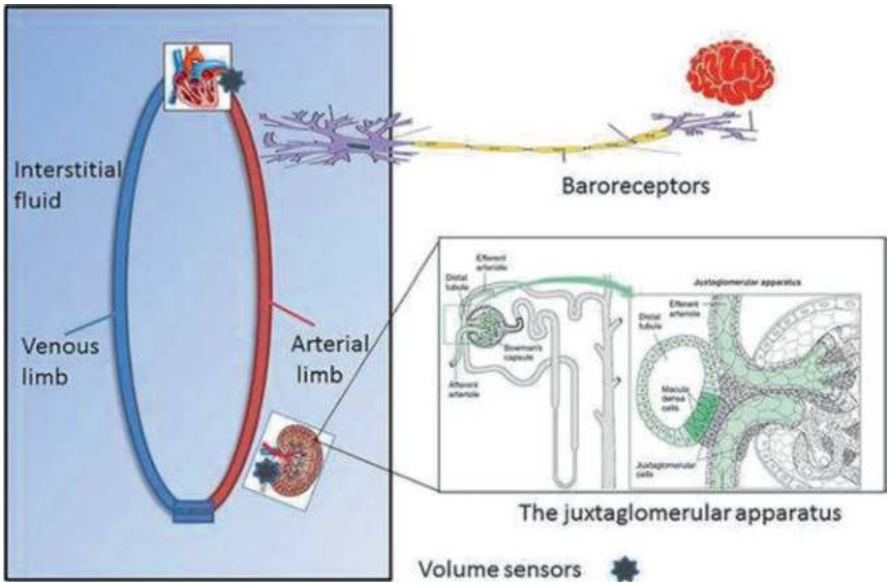

Fig. 14.2 Although the extracellular compartment is made up of the interstitial and intravascular compartments, this separation is somewhat arbitrary, since the capillary wall is highly permeable to sodium and water, and fluid continuously moves between the two compartments. No accurate mechanisms to detect extracellular fluid volume exists. Instead, the body relies on surrogate markers. The baroreceptors are pressure sensors within the vessels and ventricles, communicating via the nervous system to control sympathetic and parasympathetic excitation and regulating natriuretic hormone release. The juxtaglomerular apparatus is a flow receptor within the renal tubule and detects tubular chloride flow. These two sensing mechanisms, when activated, lead to upregulation of several effector mechanisms, including activation of the renin-angiotensin-aldosterone system, resulting in consequent sodium retention, thereby increasing the volume of the extracellular compartment

decreased renal perfusion and consequent decreased renal tubular flow, the macula densa is activated. Upon activation, the macula densa stimulates paracrine release of renin from the surrounding mesangial cells, which thereby activate angiotensin, and ultimately, aldosterone, which increases sodium reclamation in the distal collecting duct.

The relationship between tubular flow, as sensed by the macula densa, and extracellular fluid volume is complex. In some situations, the macula densa is an accurate determinant of volume status. For example, in profound diarrhea, the loss of body fluid leads to hypotension, decreased renal perfusion, decreased glomerular filtration, and consequent decreased tubular flow. The macula densa senses this low flow and appropriately stimulates the RAAS, leading to profound sodium reclamation, gradually returning the patient's body fluid status to normal.

However, consider other scenarios. For instance, in renal artery stenosis, where atherosclerotic flow limitation with the renal artery leads to a state of chronic renal underperfusion, the macula densa is similarly stimulated, leading to chronic sodium

retention and volume expansion. In this case, the patient develops hypertension and volume overload; yet, the macula densa remains underperfused, and urinary sodium will always be low. In such a scenario, interpreting a low urine sodium and increasing serum creatinine as an indication for fluid administration would be totally incorrect. Rather, diuretics are warranted. Similarly, in other states, such as congestive heart failure and cirrhosis, the macula densa senses low volume, when, in fact, the patient's extracellular volume is expanded.

In summary, baroreceptors, which are pressure receptors in the cardiac chambers and the great vessels, and the juxtaglomerular apparatus, which is a flow receptor in the renal tubule, respond to changes in blood pressure and urine tubular flow, respectively. These "sensors" control the mechanisms that regulate renal sodium retention, namely the natriuretic peptides and RAAS. But, they have no actual mechanisms to directly measure the extracellular fluid volume.

Why Positive Fluid Balance Might Be Harmful

Although the indications for fluid administration are myriad, the ultimate fate for the majority of administered fluid is the same: the extracellular compartment. Expansion of the extracellular compartment might cause hemodynamic changes in the arterial limb, as can be detected by hypertension and pulmonary edema. However, sometimes its effects are more clinically apparent in the venous limb, manifesting as elevated central venous pressure or peripheral edema. As we will discuss, arterial congestion and venous congestion are both associated with poor outcomes.

In the late nineteenth century, using isolated frog hearts, Otto Frank found that the strength of ventricular contraction was increased when the ventricle was stretched prior to contraction. This observation was extended by Ernest Starling, who in 1918, stated in his Linacre lecture on "Law of the Heart" that the energy of ventricular contraction is a function of the length of the muscle fibers prior to contraction. These studies were primarily based on ex vivo isolated myocytes, and it was not until 1954 that Sarnoff and Bergland investigated the applicability of Starling's Law in the intact circulation [39]. Using an anesthetized open chest dog model, they confirmed that increasing venous return to the heart increased stroke volume, and generated the Frank-Starling curves that we have all learned to appreciate. That important study showed that as filling pressures increased, left ventricular function increased and then plateaued. This study has frequently been cited as evidence that there is no "descending limb" of the Starling curve, even at high atrial pressures. However, there is a plateau, where further increase of filling pressure did not change stroke volume. And, interestingly, in nonhealthy animals, achieved by partial occlusion of the coronary artery, a descending limb was observed. Admittedly, a discussion about the potential downside of the Starling curve remains beyond the scope of this chapter, and consensus is unlikely to be achieved. However, whether healthy dogs (with no left ventricular descending limb) or unhealthy dogs (with a left ventricular descending limb) are more comparable to ill patients remains an unanswered question.

More recent clinical data suggests that left ventricular stretch is associated with increased mortality [40]. In observational data of hospitalized patients with decompensated heart failure, reduction of the pulmonary capillary wedge to <16 mmHg was associated with improved survival [41]. In a multicenter study of almost 400 dialysis patients, the presence of pulmonary edema was associated with an almost 400% increased adjusted risk of death compared to pulmonary edema-free patients [42]. And in critically ill patients, pulmonary edema is associated with prolonged hospital stays, mechanical ventilation, and increased mortality [43]. Thus, given extensive clinical data showing the pulmonary edema is bad, combined with questionable data regarding the downside of the left ventricular Starling curve, it seems wise to diurese patients if pulmonary edema is present. Thus, as most clinicians would agree, expansion of the arterial limb, which can lead to pulmonary edema, hypertension, and mortality, should be treated with diuretics.

More recent data has focused on the venous side of the vascular circuit, with an emerging interest in the importance of the right ventricle and venous congestion. Although the right ventricle receives considerably less attention than its larger counterpart, there are anatomical differences (Table 14.1) between the two chambers with important physiological consequences [44].

The smaller, thinner right ventricle is poised to conduit venous blood into the low-pressure pulmonary vasculature, whereby it is then delivered to the thick-walled muscular left ventricle, which can generate strong contractility to push blood into the high-pressured systemic circulation. And, while the left ventricle can respond to increased afterload, the right ventricle cannot, instead dilating and failing.

In the original Sarnoff and Bergland studies referenced earlier, the Frank-Starling curves were also generated for the right ventricle. And, unlike the equivocal results of the left ventricle, a descending limb of the right ventricle during right ventricular overload was illustrated. Presumably, increasing right ventricular wall stretch causes a paradoxical septal motion into the left ventricular space, impairing left ventricular compliance and further decreasing cardiac output [45]. In an interesting preliminary study of patients with acute right ventricular dysfunction due to pulmonary embolus, diuretic therapy was associated with an improvement of systolic blood pressure, urine output, and respiratory parameters, compared to fluid resuscitation [46], prompting a larger well-designed study of the utility of diuretics in right ventricular dysfunction [47]. Thus, it is plausible that venous congestion, which occurs either

Table 14.1 Anatomical differences between the right ventricle and the left ventricle

The right versus the left ventricle		
	Right	Left
Mass (g/m^2)	26 ± 5	87 ± 12
Wall thickness, mm	2–5	7–11
Ventricular pressures, mmHg	25/4	130/8
Stroke work index, g/m^2 per beat	8 ± 2	50 ± 20

Adapted from [44]

from right ventricular dysfunction or from excess iatrogenic fluid administration, may directly impair left ventricular function and overall hemodynamics.

In addition to the possibility of increased venous congestion impairing cardiac hemodynamics, there is a growing awareness of a potential nephrotoxic effect [48]. This knowledge dates back almost 90 years, when early physiology experiments of F. R. Winton first highlighted the importance of renal vein pressure. In an animal model, increasing pressure on the renal vein to 20 mmHg decreased urine formation, which was abolished at pressures >25 mmHg [49, 50]. Extrinsic compression of the renal veins [51] and increased intra-abdominal pressure [52, 53] have also been found to decrease renal function. Winton's classic experiments were expanded by Priebe in another early physiology experiment, studying the effect of acute renal vein and hepatic vein hypertension induced by partial balloon occlusion of the abdominal inferior vena cava in dogs. Their findings confirmed that increasing renal vein pressure decreases glomerular filtration and urinary sodium excretion, but primarily through a cardiac effect, where increased renal vein pressure simultaneously decreased stroke volume and cardiac output [54].

Despite lingering uncertainty as to whether renal vein congestion impairs renal function directly, or indirectly through its effect on the heart, a preponderance of more recent clinical data supports the early observations [55–58]. This is perhaps best studied in the scenario of the abdominal compartment syndrome in trauma patients, where increased intra-abdominal pressure increases renal vein pressures and can cause renal failure [59], which improves with decompression in some [60] but not all studies [61]. Abdominal hypertension appears to be important in nonsurgical patients too [62]. In a study of 40 patients with decompensated heart failure, 40% had abdominal hypertension, which, although asymptomatic, was associated with lower renal function despite similar cardiac output and wedge pressures [60]. In a study of almost 2600 patients undergoing right heart catheterization, increasing CVP was associated with significantly lower baseline renal function, as well as reduced survival [63]. In hospitalized heart failure patients with hemodynamic measures of both left and right heart pressures, CVP was the strongest determinant of worsening renal function [56]. In septic shock, a 1 mmHg increase in CVP was associated with a 22% increased risk of AKI [64]. In the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial, right atrial pressure was the only hemodynamic variable correlated with baseline renal function, and was associated with mortality and hospitalization [65]. Collectively, this data adds further complexity to our collective understanding of association between renal and cardiac dysfunction. Termed the "cardiorenal syndrome," and initially thought to be due to impaired cardiac output and poor renal flow, the role of venous congestion as a primary determinant of renal outcomes has emerged.

Given that peripheral edema is a manifestation of venous congestion, there is growing interest in its clinical significance. Although examining for peripheral edema is common practice, its clinical significance is less well described [66]. Current management guidelines suggest that peripheral edema is cosmetic and nonlife-threatening, and treatment recommendations range from leg elevation and

compression stockings, to dietary sodium restriction, to diuretic administration [67]. However, recent data suggests that similar to increasing CVP, increasing peripheral edema is associated with an increased risk of kidney injury [68]. In a study of almost 13,000 ICU patients, peripheral edema was present in 18%, and was associated with a 13% increased adjusted risk of developing AKI during the first 7 days of ICU care. In addition, when categorized according to the severity of peripheral edema (trace, 1+, 2+, 3+), peripheral edema severity was incrementally positively associated with AKI, as well as AKI severity. This observational study has certain important limitations. Namely, since peripheral edema is a consequence of underlying pathophysiological processes, the observed association might not be due to venous congestion per se, but rather to the underlying disease. Such residual confounding likely remains, and ultimately, further well-designed interventional studies are needed to answer these questions. However, despite the lack of conclusive evidence linking extracellular fluid accumulation to renal dysfunction, clinicians must interpret current data, no matter how limited, to inform clinical decision-making. Given the extensive observational data linking venous congestion to poor outcomes, clinicians should be cautious of the potential adverse renal effects of positive fluid balance.

Thus, in summary, whereas traditional paradigms have focused on expanding the intravascular or effective circulating volumes to maximize kidney function, a more comprehensive physiological approach acknowledges that isotonic fluid dynamically distributes across the extracellular space, and that both the volume within the arterial and venous limbs might have important clinical consequences.

The Fate of Administered Fate: Risk Factors for Fluid Retention

There have been few studies that have described the longitudinal balance of administered intravenous fluid. In a small study of patients undergoing elective major plastic surgery, which specifically excluded patients with renal disease and lacked any with heart failure, the mean operative fluid balance was 3687 ml (range 1300–8711) on postoperative day 1. Over 30% of these patients did not diurese spontaneously after the surgery, and 10% developed new heart failure, requiring fluid restriction and/or diuretics [69]. Understanding which patients spontaneously diurese administered fluid, versus which patients do not, is critical in understanding why positive fluid balance is potentially risky. In healthy individuals, saline administration leads to increased extracellular volume, which, by increasing renal tubular flow and intravascular pressure, extinguishes signalling from the juxtaglomerular apparatus within the kidney and the baroreceptors within the heart and great vessels, respectively. Consequently, the renin-angiotensin-aldosterone system (RAAS) is turned off, and natriuretic peptides increase. The collecting duct of the kidney is therefore instructed not to absorb sodium, and a natriuresis occurs. However, this normal physiological response does not occur in a wide range of pathologies. Instead, in patients with a multitude of diseases, including hypertension, systolic and diastolic left-sided heart failure, pulmonary disease, obesity, and liver disease,

the mechanisms of natriuresis in response to fluid administration are dysfunctional. In these disease states, despite marked volume overload, the "sensors" of volume (i.e., the JGA and the baroreceptors) perceive low volume states and perpetuate sodium avidity. Early physiology studies highlight this process [70]. In healthy volunteers given 60 mEq of sodium in 500 ml of fluid, plasma renin and aldosterone levels fall within minutes, resulting in rapid natriuresis, with 24 mEq of sodium excreted within 9 h and 40 mEq within 24 h. However, in volunteers with hypertension, sodium administration resulted in a "blunted" natriuretic response (only 12 mEq within the first 9 h and 29 mEq at 24 h).

Similarly, congestive heart failure, liver disease, and kidney disease are well-known sodium avid states, due to chronic activation of RAAS. Not surprisingly, these patients are at significant risk of retaining iatrogenic fluid rather than spontaneously diuresing. More recent work has also identified obesity as a primary sodium-retentive disease, which likely contributes to obesity-related hypertension [71]. Obesity frequently is complicated by hypoventilation and cor pulmonale, as well as lower circulating levels of natriuretic peptides [72], higher right-sided filling pressures [73], and a higher incidence of diuretic use [74]. Thus, in such patients with fluid-retaining tendencies, particular vigilance to fluid balance is warranted.

How Quickly to Safely Diurese: The Capillary Fluid Refill Rate

For those patients with post-illness fluid accumulation that does not spontaneously diurese, how quickly can they be safely pharmacologically diuresed? A common practice has emerged that suggests careful diuresis, in the range of 1–2 l daily, but this is not supported by clinical data. In the next section, we will summarize the literature on how quickly to diurese patients.

Diuretics block sodium reclamation through one of several transport mechanism in the renal tubule, as well as interrupting water handling. The consequence of active diuresis is isotonic fluid loss, namely equal proportions of sodium and water loss as compared to the rest of the body. This isotonic fluid is primarily lost from the circulating vascular fluid compartment. With time, fluid moves from the interstitium into the vascular space, a process termed "vascular refill." This refill process depends on the movement across the capillary wall and varies with the degree of interstitial congestion. In addition, sympathetic tone and intrinsic cardiac function are both important determinants of the refill rate.

The concern for overaggressive diuresis is that the vascular refill rate will be exceeded, leading to intravascular depletion, hemodynamic collapse, and consequent hypoperfusion of vital organs. A common practice has emerged to diurese "1–2 liters a day," but is not supported by data. Much has been learned about the refill rate from the dialysis literature, where fluid is actively and aggressively removed directly from the circulating intravascular volume [75]. In a typical dialysis session of 4 h, as much as 4–6 l can be removed from reasonably healthy patients. Given that the total intravascular volume is approximately 5–7 l, vascular refill obviously occurs quickly, and in healthy individuals, it is considered to be

approximately 1 l/h. The refill rate has also been described in sicker patients. In a study of severe New York Heart Association Class IV heart failure patients, the refill rate was as much as 600 cc/min, decreasing to approximately 300 cc/min with 4 l of dialytic fluid removal [76]. More aggressive diuretic regimens have been associated with a reduction in mortality [77]. Thus, the adage of "1–2 liters" per day as a diuresis goal is likely too conservative and leads to significant underdiuresis. In the setting of limited resources that curtail lengthy hospitalizations, patience for slow diuresis has evaporated, and more often than not, continued diuresis is left to the outpatient setting. In such an unmonitored setting, the efficacy and safety of diuresis are unclear.

Diuresis goals should be patient-specific and titrated to patient hemodynamics rather than a specific fluid removal rate. Given that the most important indicator of the refill rate is systolic blood pressure, blood pressures should be followed carefully, and antihypertensive medications, particularly ace-inhibitors, should be stopped. Other medications that modulate the renal perfusion, such as nonsteroidal anti-inflammatory drugs, should also be avoided during diuresis. If hypotension occurs, diuresis should be slowed, but otherwise, more aggressive diuresis than current practice is likely warranted.

Clinical Correlation

Fluid remains an important part of early resuscitation in critically ill patients, distributing into the extracellular compartment. For some individuals without fluid-retaining tendencies, this iatrogenic fluid is likely spontaneously diuresed after illness resolution. But for those with a wide range of fluid-retentive tendencies, such as heart failure, renal disease, obesity, and pulmonary disease, it is likely that administered fluid accumulates. The potential negative effect of such fluid accumulation is myriad, as summarized in Fig. 14.3. Expansion of the arterial circuit leads to hypertension and pulmonary edema. Expansion of the venous circuit leads to swelling of the encapsulated organs, such as the kidney and liver, and has been associated with acute kidney injury and increased risk of mortality. Fluid accumulation within the soft tissue increases the risk of skin breakdown and pressure ulcers, not to mention decreased mobility, increased challenges with mechanical ventilation, and probable risk of iatrogenic complications.

Despite an absence of rigorous data addressing the best method to prevent fluid overload in critically ill patients, we are charged with taking care of patients, and must use the current evidence combined with our collective clinical judgment. In my opinion, more aggressive use of diuretics is warranted in the care of any patient who does not achieve euvolemia after stabilization. Euvolemia is determined by the absence of peripheral edema in the great majority of patients, and all patients should have admission and discharge weights. Awareness of the complications of fluid retention could lead to more liberal use of vasopressors or toleration of lower mean arterial pressures, approaches that ultimately will require careful oversight and scrutiny, yet given the obvious risk with fluid accumulation, might be warranted.

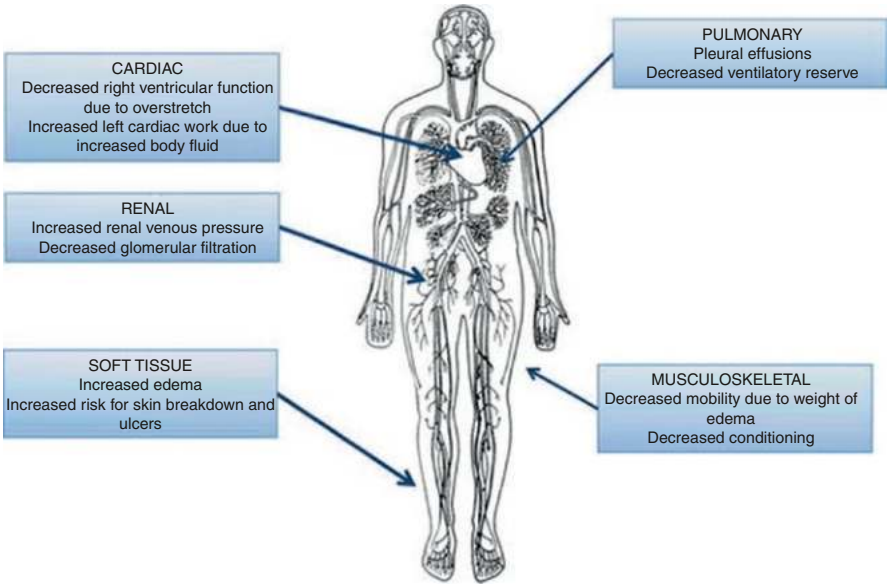

Fig. 14.3 Potential effects of positive fluid balance. Increased extracellular fluid will ultimately distribute into the vascular and interstitial spaces, with potential negative sequelae across multiple organ systems. Venous congestion likely impairs right ventricular function by overstretching the right ventricle, and potentially impairs left function by paradoxical septal movement. In addition, increased renal venous pressure might decrease the glomerular filtration rate. Retained soft tissue fluid is likely associated with a greater risk of skin breakdown and patient immobility, and thus ulcer formation. Increasing body weight due to fluid retention likely leads to decreased patient conditioning and increased cardiopulmonary demand

Conclusion

The preponderance of observational data suggests that positive fluid balance has the potential for causing harm, particularly in those patients with a predisposition to fluid retention. A paucity of well-designed studies to more fully address this association cannot free providers from making decisions about fluid balance, and until more rigorous studies have been completed, providers should at the very least carefully track fluid balance and weight changes within the hospital stay, and perhaps consider pharmacological diuresis to reestablish euvolemia prior to discharge.

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Fluid Management and Its Role in Enhanced Recovery

15

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Abstract

Enhanced recovery programs have repeatedly been shown to safely reduce perioperative morbidity and hospital length of stay for surgical patients, and are steadily becoming standard practice across an increasing number of surgical specialties. For these programs to be successful, appropriate fluid management is essential throughout the whole perioperative period with the main aim being to maintain physiological normality for patients wherever possible. While excessive fluid administration increases the risk of harm through tissue edema and surgical ileus formation, insufficient fluid administration will result in end-organ failure. To minimize these risks, patients should start surgery minimally dehydrated, be given fluids to replace what is lost intraoperatively, and then converted to normal enteral intake again as soon as possible after the operation is finished. Good clinical assessment is essential throughout the perioperative period to evaluate how fluid-responsive the patient is at that time and whether they would benefit from further volume, or more inotropic support instead. Increasingly in mechanically ventilated patients, dynamic markers such as stroke volume variation have been shown to be the most effective way of doing this, although these measures do have a number of limitations that need careful consideration.

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Another approach is targeting fluid administration to a patient's cardiac output—so-called "goal-directed therapy." Again, there is good evidence that like enhanced recovery pathways, goal-directed therapy can also reduce perioperative morbidity and surgical patient's length of stay. National guidelines currently recommend that every surgical patient should have an individualized fluid plan as part of their enhanced recovery program and that goal-directed therapy should be considered as part of this approach—particularly in either high-risk patients and/or more major surgical procedures.

Key Points

1. Enhanced recovery pathways are multidisciplinary care pathways that have repeatedly been shown to safely reduce postoperative morbidity and hospital length of stay.
2. Appropriate, individualized fluid management is essential to a successful enhanced recovery approach and needs to be continued throughout the whole perioperative period.
3. Preoperatively, patients should not be excessively starved or dehydrated, that is, avoid unnecessary mechanical bowel preparation, solids to 6 h pre-op, a carbohydrate drink, and clear fluids up to 2 h pre-op.
4. A goal-directed approach should guide intraoperative fluid management in moderate- to high-risk cases with the aim of giving the least amount of fluid required to maintain optimal blood volume and cardiac output.
5. Oral fluid should be encouraged and intravenous (IV) fluids discontinued as soon as possible postoperatively to minimize the risk of further complications. If an IV is needed post-op, beware of ongoing salt loading. Saline, Ringer's lactate, or Hartmann's are NOT maintenance fluids.

Introduction

In the late 1990s, professors Wilmore and Kehlet in Boston and Denmark developed a care pathway for colorectal patients undergoing major elective surgery with the aim of minimizing post-op morbidity and hospital length of stay. This pathway incorporated a number of different and wide-ranging interventions based on the best evidence available at that time [1, 2].

Similar "fast-track" pathways have since developed all over the world with various names. In the United Kingdom, this pathway is known simply as enhanced recovery, and since its first launch in the mid 2000s, enhanced recovery pathways have now become commonplace among many surgical specialties in most British hospitals [3]. While the strongest evidence base perhaps remains in colorectal surgery where the pathway has been running the longest, elective orthopedic joint replacements, major gynecological surgery, and urological teams were also quick to

adopt similar schemes, and the evidence base in each of these specialties is now growing as well [3].

The Benefits of Enhanced Recovery Pathways

A number of different systematic reviews have now shown that fast-track surgery programs can successfully reduce length of stay in colorectal patients, even though mortality rates remain unchanged [4–8]. In 2010, a meta-analysis of six randomized control trials (RCTs), which used between four and nine different enhanced recovery pathway elements, showed that enhanced recovery pathways significantly reduced length of stay by at least 2 days and complication rates by 50% [8]. A second independent systematic review in 2011 drew almost identical conclusions [7]. Despite encouraging earlier discharges, most studies suggest that enhanced recovery pathways do not result in increased numbers of readmissions at 30 days [6, 9].

Similar results are starting to be seen in other surgical specialties as well. A systematic review into enhanced recovery use in urological surgery in 2015 identified six studies and concluded that enhanced recovery reduced patient stay without increasing morbidity or mortality [10]. However, a similar Cochrane review into enhanced recovery use in gynecological oncology surgery, which was updated in 2014, failed to identify any RCTs that met their inclusion criteria [11]. Although, other nonrandomized control trials have shown similar decreases in length of stay with enhanced recovery use in gynecology as well. For example, an observational study in Sweden, published in 2014, showed that 17% more women were discharged within 2 days of an abdominal hysterectomy immediately after the introduction of an enhanced recovery pathway [12]. Two recent systematic reviews have examined enhanced recovery use in upper gastrointestinal surgery; Gemmill et al. concluded after reviewing 18 eligible studies (including three RCTs) that enhanced recovery appeared safe and might reduce length of stay in patients undergoing surgery for both gastric and esophageal cancer, but the evidence base remained weak [13]. Meanwhile, Beamish et al. identified 14 studies (including nine RCTs), with a total of 1676 patients with gastric cancer. They concluded that enhanced recovery pathways were safe, feasible, and cost-effective, with a nonsignificant trend toward reduced length of hospital stay [14].

The largest study to investigate the effect of enhanced recovery programs so far is a recently published three-year cross-specialty national audit conducted by the Enhanced Recovery Partnership Programme. Four surgical specialties were audited (colorectal, urology, orthopedic, and gynecology) in 61 British hospital trusts from 2009 to 2012, with a weak correlation seen between enhanced recovery pathway compliance and reduced length of stay in colorectal, orthopedic, and gynecological surgeries. The median lengths of stay in colorectal, orthopedic, and gynecological surgeries reduced by 2, 3, and 4 days, respectively, over this period, with no change in length of stay seen in gynecology [15].

Components of Enhanced Recovery Pathways

Kehlet's initial pathway focused on minimizing the effects of the surgical stress response through improving analgesia, using short-acting anesthetics (or where possible regional anesthesia) and minimally invasive surgery, and encouraging early mobilization and nutrition [1, 2].

While the specific components of any particular enhanced recovery pathway vary between different hospitals and different surgical specialties, the majority of the interventions remain remarkably consistent, and fluid therapy is always one of the major components.

The requirements of what the UK Enhanced Recovery Partnership Programme specify should be included in a typical enhanced recovery pathway are shown in Table 15.1 [3, 16]. Fluid therapy is clearly mentioned (and highlighted) in each of the three stages of the table (preoperatively, intraoperatively, as well as postoperatively).

While it is now widely accepted that enhanced recovery pathways can safely reduce hospital length of stay, it remains controversial as to which elements in the enhanced recovery approach are most important in achieving this [3]. Even though a recent systematic review found no evidence that goal-directed fluid therapy impacts C-reactive protein (CRP) values [17], given that fluid management still varies greatly between different centers and different clinicians [18, 19], and different fluid protocols can greatly impact surgical complication rates (possibly by as much as nearly 50% [20]), it seems reasonable to propose that optimal perioperative fluid

Table 15.1 Components of a typical enhanced recovery pathway

Enhanced recovery elements as suggested by the UK Enhanced Recovery Partnership Programme		
Preoperative	Intraoperative	Postoperative
Pre-op visit	Antibiotics prior to first incision	Nasogastric tube removal
Patient assessed for surgery	Epidural or regional analgesia	*Avoid crystalloid overload*
Patient explanation of enhanced recovery	*Use fluid management technologies to individualize fluid therapy*	*Use a "goal-directed" style of fluid management*
Education given (e.g., therapy in MSK or stoma in colorectal)	*Avoid excess crystalloids*	Post-op nutrition (encourage early oral intake)
Oral bowel prep avoided	Hypothermia avoidance	Nausea and vomiting control
Admitted on day of surgery	Avoid abdominal drains	Early mobilization
Carbohydrate drinks given		Early removal of catheter
Maintain good pre-op hydration		Avoid systemic opiates
Avoidance of sedatives		

Adapted from [3, 16]
MSK musculoskeletal

management should be an essential component of any enhanced recovery protocol. The challenge is in defining what constitutes "optimal."

Fluid Therapy in Enhanced Recovery: The Optimal Approach

Perioperative fluid management is an important consideration throughout the whole surgical pathway, and optimal fluid management should be viewed as a continuum throughout the patient's whole hospital admission. Suboptimal management at any point will not only lead to significantly longer hospital admissions, but also risks compromising the benefits conferred by other elements of the enhanced recovery package [21].

The overarching focus—as with many enhanced recovery elements—should be to always aim for as near physiological normality as possible. In the context of fluids, this can be thought of as avoiding dehydration and hypovolemia or fluid overload with their associated complications. Inadequate fluid administration results in insufficient perfusion pressures, reducing oxygen delivery and increasing anaerobic metabolism, which ultimately leads to cell death and end-organ failure [22]. One of the most common perioperative manifestations of this is probably acute kidney injury (AKI).

Conversely, excess fluid administration can have equally harmful consequences, raising hydrostatic pressures and increasing levels of atrial-natriuretic peptides, which damage the delicate glycocalyx layer of the vascular endothelium [22]. This renders blood vessels "leaky" and causes damaging tissue edema to develop in the interstitium, which again impairs tissue and organ oxygenation [22]. This interstitial edema, together with high salt loads from excess crystalloid infusion, can also lead to postoperative ileus and further increase patient's length of stay [23]. See Fig. 15.1 [24].

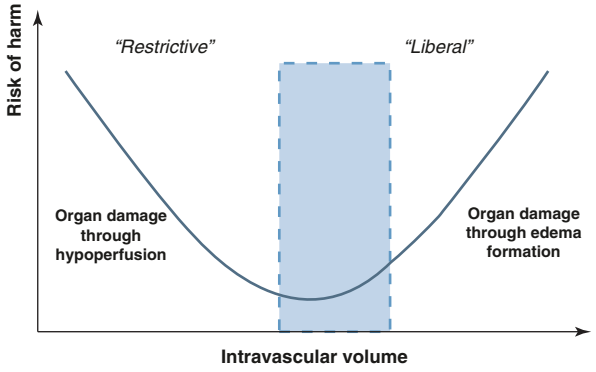

Fig. 15.1 Both "restrictive" and "liberal" fluid administration increase the risk of end-organ damage through hypoperfusion or tissue edema generation, respectively. To avoid being overly restrictive, clinicians should aim for a "moderately liberal" approach (shown shaded) where the patient will finish surgery approximately 1–2 litres positive (Adapted from [24])

Unfortunately, terminology in this area has often been confusing historically. "Liberal fluid therapy" was initially encouraged perioperatively to maintain a proposed "third space." However, evidence to support this theoretical compartment has always been scarce, and as our understanding about glycocalyx damage and resulting interstitial edema (as explained previously) increased, consensus has shifted toward using a more "restrictive" approach to fluid administration [25]. Yet, the term "restrictive" suggests tending toward an equally damaging hypovolemic state. Recent reviews have since proposed abolishing the terms "restrictive" and "liberal", and instead using the phrase "zero-balance" to avoid these misinterpretations and encourage a moderately restrictive approach that aimed avoid excessive fluid retention and weight gain by only replacing what is lost (e.g., insensible loss through ventilation and respiration, or volume loss from intraoperative hemorrhage) [21, 24]. However, in 2018 the large multi-centre trial 'Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery (RELIEF)' reported that, compared to a more liberal approach, restrictive approaches to fluid therapy were associated with higher rates of Acute Kidney Injury (AKI) (8.6% vs 5.0%, $p < 0.001$), renal replacement therapy (0.9% vs 0.3%, $p = 0.048$) and septic complications or death (21.8% vs 19.8%, $p = 0.19$) [26]. In this study the restrictive and the liberal groups received 1.7 or 3.3 litres of intraoperative fluid respectively and median length of surgery was 3.3 h in both groups; suggesting that aiming for a 'zero balanced' approach might actually lead perioperative physicians to tend towards being too restrictive with fluid administration [27].

Subsequently, clinicians are now being encouraged to aim for a 'moderately liberal fluid regimen' throughout the perioperative period. As different considerations arise during the preoperative, intraoperative, and postoperative phases of surgery, the next sections will consider how this approach should be applied to each of these in turn.

Preoperative Fluid Management

The main aim with preoperative fluid management is to prevent patients from becoming dehydrated before the surgery even starts. It is clearly much easier to manage ongoing fluid administration intraoperatively if the patient starts their operation in a normal euvolemic state [21]. However, although this concept sounds straightforward, there are a surprising number of challenges to achieving this in practice.

While patients evidently need to avoid solid food for elective procedures to minimize the risk of aspiration on induction, increasingly international guidelines are recognizing the importance of not prolonging this fasting period for fluids further than 2 h prior to surgery. Cochrane reviews have shown that drinking clear fluids up until 2 h before surgery is not associated with an increased risk of aspiration or other complications in either adults or children. If anything, these reviews suggest that drinking clear fluids actually reduced adult gastric volumes and made the preoperative experience more comfortable for both adults and children [28, 29]. The

European Society of Anaesthesiology also now encourages both adults and children to drink fluids up to 2 h preoperatively in its guidelines [30], as does the American Society for Enhanced Recovery (ASER) & Perioperative Quality Initiative (POQI) joint consensus statement on perioperative fluid management within an enhanced recovery pathway for colorectal surgery [31].

Many enhanced recovery protocols also encourage the avoidance of mechanical bowel preparation in many patients for similar reasons, although this is becoming more controversial. Mechanical bowel preparations have been shown to increase dehydration and decrease patient's comfort, without reducing the risk of early postoperative complications in the majority of cases [32–34]. However, some surgeons think that mechanical bowel preparation does make certain procedures easier, particularly laparoscopic cases, and some recent evidence suggests that mechanical bowel preparation may significantly improve 10-year survival data in elective colorectal cancer cases [35, 36]. Overall though, avoiding mechanical bowel preparation currently remains an essential part of the enhanced recovery package because of the significant effects the preparation can have on preoperative hydration status.

As well as being well hydrated preoperatively, patients' nutritional status should also be optimized prior to surgery using carbohydrate energy drinks (containing at least 45 g carbohydrate) [31]. These drinks also decrease patient discomfort while waiting for surgery as well as decreasing postoperative insulin resistance through increasing insulin activity [37, 38]. They can safely be taken 2–3 h prior to surgery depending on the nutritional content [39].

Intraoperative Fluid Management

Again, as with most other enhanced recovery elements, the main aims of intraoperative fluid balance in enhanced recovery pathways should be to maintain physiological normality as much as possible, that is, to maintain euvolemia and minimize electrolyte disturbance. Successful preoperative fluid management should allow the patient to start surgery well hydrated, meaning that the main intraoperative aims are simply to replace ongoing losses without giving excess salt or water [21], aiming to finish 1–2 litres positive balance overall to prevent against harm associated with restrictive fluid regimens [26, 40].

Insensible losses (e.g., perspiration or urine output) will make up a very small percentage of ongoing losses, and these will need replacing with a maintenance fluid regime, often using crystalloids. Direct measurements of intraoperative evaporative losses have shown this to normally be less than 1 ml/kg/h in normal conditions, and it is important to remember that giving fluids in significant excess of this rate can rapidly lead to harm and postoperative complications (such as ileus as explained earlier) [23, 41]. However, an overly restrictive intra-operative fluid regime can lead to higher rates of acute kidney injury and current consensus is that perioperative physicians should target a moderately liberal intraoperative balance, with an overall infusion rate of around 10–12 ml/kg/hr crystalloids during major abdominal surgery [26, 27].

The majority of ongoing intraoperative losses, however, will be intravascular volume losses. For example, the patient could lose volume through blood loss or from compartmental fluid shifts, such as interstitial edema formation, secondary to the surgical inflammatory response [21, 22]. These losses will require replacement with equivalent volumes of similar fluids (e.g. blood loss should ideally be replaced with blood products, including platelets and clotting factors in the event of significant hemorrhage) [22].

While heavy blood loss may be easy to see if the suction equipment is rapidly filling in the operating theater, intercompartmental shifts may be much less obvious to either the surgeon or the anesthetist. If volume loss is suspected, then a "volume challenge" or "fluid challenge" should be used to see if there is any evidence of intravascular depletion, which might respond to further filling.

The fluid challenge remains one of the singlemost important tools for the anesthetist in assessing fluid responsiveness [42]. If the patient is fluid-deplete and can tolerate further fluids, then a small but rapid fluid bolus should increase preload enough to cause a measurable increase in stroke volume and therefore cardiac output. A positive response proves that the patient is "fluid (or volume) responsive" [42].

A typical fluid challenge would be 500 ml of fluid given rapidly over 5–10 min, and a fluid-responsive patient should increase their stroke volume by at least 10–15% in response to this [21, 43, 44].

Another simple way of testing fluid responsiveness is with a passive leg raise (PLR), where the legs are lifted above the height of the heart. This generates a similar response to a traditional fluid challenge by increasing venous return (and preload) by moving blood out of the venous system in the legs [45]. While rarely of use during surgery, this maneuver has a place in the assessment of volume status following surgery.

However, it is essential to remember that "fluid responsiveness" and "hemodynamic instability" are not interchangeable or equivalent. Around half of all hemodynamically unstable critically ill patients were still not responding to fluid alone—they will not be "volume-responsive," and they may also require treatments with vasopressors to increase systemic resistance, or inotropes to increase contractility [44]. Equally, a volume-responsive patient will not always be intravascularly fluid-deplete [21]. Patients in successful enhanced recovery pathways should normally be less fluid-responsive than other patients, as they more likely start their operation well hydrated [42].

The whole clinical picture should always be viewed in context when assessing for fluid responsiveness, and hence a good clinical assessment is vital for correct decisions on intraoperative fluid management (see section on 'clinical assessment of fluid status' later in chapter) .

Postoperative Fluid Management

Postoperatively, patients should be encouraged to restart normal oral food and fluids as early as possible in enhanced recovery pathways, and intravenous fluids should be stopped as soon as this is achieved. Continuing intravenous fluids into the postoperative phase further increases the risk of developing postoperative ileus as

explained earlier, particularly as patients' ability to excrete and remove both sodium and chloride is reduced postoperatively [23]. For this reason, if fluids are required to continue postoperatively, then low-volume fluids with relatively low sodium contents should be considered—particularly, when most patients will already have been given an excess of sodium and chloride intraoperatively [21].

Continuing intravenous fluid postoperatively will also have negative consequences on other enhanced recovery pathway elements. One of the main focuses of enhanced recovery in the postoperative phase is to encourage early mobility, and patients are inherently less likely to mobilize if they are connected to intravenous fluid lines. Equally, catheters will also discourage patients from mobilizing, and should be removed as soon as possible [21]. Adequate analgesia is also important to maximize the chances of early mobilization, but laxatives may also be required to minimize constipation and urinary retention depending on the surgical procedure that has been performed.

Early oral intake also has independent surgical benefits. A systematic review has shown that early feeding significantly reduces the risk of postoperative infection and also independently reduces hospital length of stay. In addition, it may lower the risk of surgical anastomotic dehiscence, wound infection, pneumonia, intra-abdominal abscess, and mortality, although these did not reach statistical significance in the meta-analysis performed [46]. In the UK and USA now, perioperative physicians are increainsgly being encouraged to get their patients to 'DREAMing' in order to achieve these goals, with the 'DREAM' acronym standing for getting patients 'DRinking, Eating And Mobilising' as soon as possible after surgery [47].

Clearly, how fluids are managed throughout the preoperative and intraoperative phases will impact how the postoperative phase is managed and how successful the enhanced recovery fluid regime will be overall. For example, failing to prevent preoperative dehydration would mean the patient would already start the intraoperative stage with a relative fluid deficit and require larger volumes of fluids intraoperatively, increasing the risk of ileus postoperatively and delaying the patient's discharge.

The Need to Individualize Fluid Therapy

While the same general principles will need to be applied throughout every patient's perioperative pathway, the exact management cannot be completely protocolized in advance as it will always differ from patient to patient, from operation to operation, and in some cases between different anesthetic techniques [48].

In other words, an *individualized* approach to fluids is required for each operation, which means that a way of continuously assessing and reassessing an individual patient's fluid requirements throughout the whole perioperative period is essential.

Clinical Assessment of Fluid Status

Assessing a patient's fluid status is an essential clinical skill that is taught from the very first days of medical school. There are a number of different physiological

markers that clinicians are traditionally taught to use to monitor fluid status. Some examples of clinical signs and parameters that might suggest a patient is hypovolemic are as follows:

- Heart rate above 90 (or n % > baseline)
- Systolic blood pressure below 90 (or n % < baseline)
- Urine output of less than 0.5 ml/kg/h
- High lactate
- Low central venous pressure

However, it is becoming increasingly clear that none of these markers are completely reliable indicators of an anesthetized patient's fluid status [21]. Many are not specific. For example, a heart rate over 90 could be expected in any type of systemic inflammatory response (historically referred to as the "SIRS criteria"). Although SIRS was originally defined to identify sepsis, it could equally be a response to trauma, inflammation, or ischemia among other things—in fact, over 80% of surgical intensive care patients would meet the SIRS criteria [49, 50], hence these criteria are no longer used to define sepsis in critical care [51].

Many of these markers are also not very sensitive for detecting changes in volume status, partly due to a confounding effect of the normal physiological response to systemic blood loss, which is constriction of the splanchnic circulation. Splanchnic vasoconstriction has a protective physiological effect by moving blood back into the systemic circulation and maintaining vital organ perfusion. However, because this means that the systemic circulation is relatively maintained, heart rate and blood pressure do not alter dramatically, even in the presence of large overall volume deficits. These variables only start to change when the volume deficit cannot be contained within the splanchnic circulation alone [21]. For example, in one study where young healthy volunteers gradually had 25% of their total blood volume removed by phlebotomy over an hour, the only significant marker to change was gastric tonometry—a specific monitor of splanchnic perfusion. Heart rate and mean arterial blood pressures remained unchanged on average, despite this large volume loss [52].

Urine output is another measure that is often taught as being a good marker of volume status and a relatively simple way of approximating kidney function. However, urine output is often poorly recorded both intraoperatively and postoperatively, and intraoperative oliguria (i.e., urine output <0.5 ml/kg/h) is not predictive of developing acute kidney injury or of overall volume status in patients undergoing major noncardiac surgery [53].

Likewise, hourly monitoring of central venous pressure (i.e., the pressure recorded from either the right atrium or the superior vena cava) was routine in intensive care units all over the world in the late 1990s and early 2000s. However, in 2008, a systematic review of 24 studies concluded that central venous pressure was actually a very poor predictor of which patients needed more fluid and also of an individual patient's overall blood volume. The authors recommended that routine central venous pressure monitoring should no longer be performed perioperatively [54].

Transesophageal echocardiography has also been trialed as a method for assessing volume status. The principle seems particularly appealing as it allows direct visualization of the heart itself, and it is relatively simple to perform in an anesthetized patient. Yet, measurements of both right and left end-diastolic volumes are variable, and, as with many of the static variables described previously, have ultimately proved to not be helpful in assessing a patient's fluid responsiveness [55, 56].

However, using ultrasound to measure the *change* in diameter of either the inferior or superior vena cava has been shown to be very predictive in assessing fluid responsiveness of patients undergoing positive pressure ventilation [56]. Measuring the change in diameter makes this a dynamic marker and, indeed, many other dynamic variables have also been shown to be useful in assessing fluid responsiveness, particularly in mechanically ventilated patients.

Using Dynamic Variables to Assess Fluid Status

Using dynamic indicators to assess fluid responsiveness has repeatedly been shown to be more effective than using static markers [42, 45, 55]. This conclusion was supported by the findings of a systematic review comparing static and dynamic indices. Many of the dynamic variables used in this review were related to pressure changes at different points of the respiratory cycle, for example, pulse pressure variation [55].

Pulse pressure variation (see Fig. 15.2) is produced by changes in venous return (cardiac preload) at different points in the respiratory cycle if the patient is mechanically ventilated. This is due to the right atrial pressure increasing during positive pressure inspiration and decreasing again in expiration. These pressure changes cause cyclical changes to venous return and to ventricular filling pressures [45].

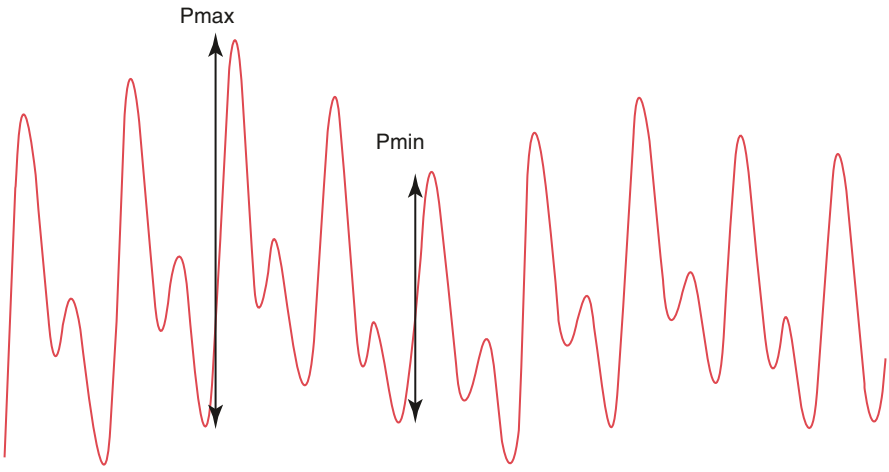

Fig. 15.2 Pulse pressure variation is the percentage difference between the maximum pulse pressure (P_{max}) and the minimum pulse pressure (P_{min})

These changes are also greater in volume-depleted and fluid-responsive patients, giving a very accurate measure of fluid responsiveness. Pulse pressure variation is relatively easy to visualize on a normal arterial pulse pressure trace too, making it a very useful measure of fluid responsiveness in mechanically ventilated patients with an arterial line in situ [57]. In general, a pulse pressure variation of at least 13% will predict a 15% or greater increase in cardiac output in response to a 500 ml bolus of crystalloid [45].

Similar cyclical changes can be seen in the oxygen plethysmography trace. These plethysmography variations have been shown to approximate well to the pulse pressure variations described earlier, with a plethysmography variation over 15% accurately predicting a pulse pressure variation over 13%. The big advantage of using plethysmography variation over pulse pressure variation is that it can be measured noninvasively through a normal oxygen saturation finger probe and no invasive lines are required [58, 59].

As the main determinant of pulse pressure is stroke volume, it is not surprising that similar variations in stroke volume are also seen in mechanically ventilated patients and can also be used as an accurate predictor of fluid responsiveness. Stroke volume variation can be measured using transesophageal echocardiography, and dedicated transesophageal Doppler probes are now recommended by the National Institute of Clinical Excellence and routinely used throughout the United Kingdom for this purpose [45, 55, 60].

Although being very accurate, all of these different variations rely on a number of assumptions. For instance, patients must be mechanically ventilated with normal intrathoracic and abdominal pressures to ensure these respiratory pressure changes cycle appropriately. The patient must also be in sinus rhythm, as other rhythms such as atrial fibrillation (with an irregular R-wave to R-wave time) will affect how the intrathoracic pressure cycles are transduced at the right atrium, and the ventricles and smaller tidal volumes will reduce these pressure changes, again altering the test's predictive value significantly [21, 45, 57]. Some of these factors will cause pulse pressure variation to appear artificially large (false-positive), while others will cause a decrease in variation size despite no change in fluid responsiveness (false-negative). The acronym "LIMITS" offers one way of remembering these effects [61]. See Fig. 15.3 [61].

Ultimately, both pulse pressure and oxygen plethysmography variations are simply less invasive ways of indirectly measuring stroke volume variation. As a successful fluid challenge is one that results in an increase in stroke volume (and therefore cardiac output) as explained earlier, fluid therapy should always be targeted to increase stroke volume and not thought of as reducing oxygen plethysmography or pulse pressure variation.

Whereas previously standard (static) ways of assessing fluid status left no clear end point, and it was often very challenging to know whether fluid administration had been beneficial or not, with dynamic assessment of stroke volume variation there is a very clear end goal to fluid therapy: a measurable increase in stroke volume and cardiac output [21, 44, 55].

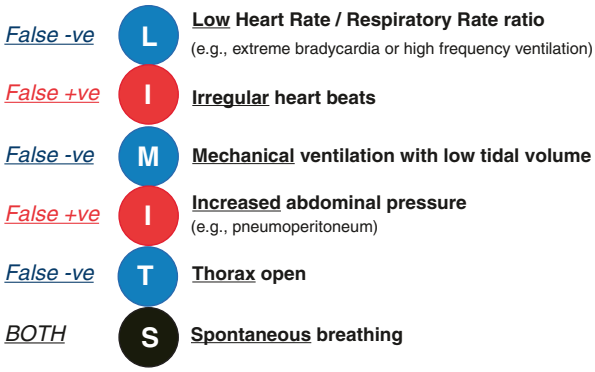

Fig. 15.3 The "LIMITS" to using pulse-pressure variation monitoring, and whether a false-positive or false-negative result should be expected in each case (Adapted from [61])

This concept has led to whole new method of giving fluids known as "goal-directed fluid therapy," which is increasingly being used in many enhanced recovery pathways around the world [21, 62].

Goal-Directed Fluid Therapy

Goal-directed fluid therapy can be defined as using fluids, vasopressors, and/or inotropic agents to increase cardiac output and therefore tissue oxygen delivery. Fluid administration would achieve this aim normally through increasing preload and consequently stroke volume as explained previously.

The concept was developed more than 30 years ago after the invention of the Swan–Ganz pulmonary artery catheter in the early 1970s allowed rapid changes in cardiac output to be measured for the first time [63, 64]. Soon after this, in 1978, Bland *et al*. proposed that oxygen delivery would be a useful therapeutic goal to target [65]. In 1988, Shoemaker *et al*. used a protocol with the pulmonary artery catheter to target increased oxygen delivery and showed that this significantly reduced mortality in high-risk surgical patients—a concept that we continue to use today [66].

Since then the pulmonary artery catheter has gone from being a common sight in most critical care units to now hardly being used at all. This is partly due to the many risks associated with its use, and also because a number of other reliable, less invasive, and less risky cardiac output monitors have since entered the market [67].

Different ways of monitoring cardiac output include everything from using routine monitoring to visualizing changes in the stroke volume, pulse pressure, or oxygen plethysmography variations as described above, through to specially designed devices such as the esophageal Doppler mentioned earlier or lithium-dilution cardiac output monitoring devices such as the LiDCOrapid device (LiDCO, Cambridge, UK). This device injects a small bolus of lithium and uses this together with the arterial waveform trace to give a calibrated beat-by-beat estimate of cardiac output [60, 68, 69].

Goal-directed therapy approaches are now widely used in Australia, New Zealand, the United States of America, and particularly in the United Kingdom where the esophageal Doppler device remains the most common method of monitoring cardiac output changes [68].

In 2012, a Cochrane systematic review of 31 trials with a total of more than 5000 patients concluded that goal-directed fluid therapy significantly reduced morbidity in elective surgery. The rates of acute kidney injury, respiratory complications, and wound infections were all significantly reduced when goal-directed fluid therapy was used; the length of hospital stay was also 1 day shorter on average, and overall, fewer patients suffered complications. The review found no evidence to suggest any potential harm through using goal-directed therapy, and although there were hints of a possible downward trend in 28-day mortality, this did not reach significance (28 day mortality = 7/100 in control, 6/100 in GDFT arm, RR = 0.81, CI 0.65–1.00) [70].

Overall, these conclusions were very similar to the effects seen in studies looking at the benefits of enhanced recovery pathways as described earlier—both interventions have been shown to significantly reduce morbidity and length of stay in surgical patients, but have not been shown to significantly impact the mortality of these patients [8, 70].

Goal-Directed Fluid Therapy in Enhanced Recovery Protocols

A number of recent studies have specifically tried to assess the benefits of using goal-directed fluid therapy within an enhanced recovery protocol, but overall the results have been mixed.

In 2012, Brandstrup *et al*. randomized 150 elective colorectal patients in an enhanced recovery pathway to receive either fluid therapy guided by an esophageal Doppler or to receive a zero-balance fluid therapy approach. No significant difference between the two groups was seen at 30 days for major or minor complications, mortality, or hospital length of stay [71] .

Srinivasa *et al*. conducted a similar trial in 2013 in 85 elective colorectal patients who were all part of an enhanced recovery protocol that included a preoperative drink and avoidance of prolonged fasting. Half of the patients received "restrictive fluid management" (maximum 1500 ml intraoperatively) and the other half received goal-directed therapy. Again, median lengths of stay and number of complications were almost identical between both groups (6 vs 5 days, and 26 vs 27 developed complications). Interestingly, the amount of intraoperative fluids administered to each group was also similar: 1994 ml in the goal-directed fluid group compared to 1614 ml on average in the restrictive group, and there was no clinically relevant difference in the hemodynamic variables [72].

In 2014, Phan *et al*. again randomized 100 elective colorectal patients so that 50 received a restrictive approach and 50 received fluids based on esophageal Doppler guidance. All 100 patients otherwise followed an identical enhanced recovery protocol. Again, there was no difference in the median length of stay (6 days in the

restrictive group compared to 6.5 in the goal-directed group, $p = 0.421$) or rate of complications (52% in restrictive compared to 60% in goal-directed, $p = 0.42$). In this case, the two groups did receive a statistically different amount of fluid intraoperatively, but both still received relatively small overall volumes (1500 ml in the restrictive compared to 2190 ml in the goal-directed group, $p = 0.008$) [73].

In a similar randomized trial in 2015, Lai *et al*. looked at 220 enhanced recovery patients having either rectal resections or cystectomy with ileal conduit operations and again randomized them to receive either goal-directed fluid therapy using colloid fluids guided by the LiDCO rapid or a relatively liberal control group. Interestingly, this group also stratified their samples by preoperative fitness using cardiopulmonary exercise testing. Despite the goal-directed (intervention) group receiving an average of 956 ml more Gelofusine (B. Braun, Melsungen, Germany), no significant differences were seen in either mean length of stay (9.6 days control to 11.8 days intervention, $p = 0.091$) or postoperative complication rates (48.6% control vs 50.5% intervention, $p = 0.717$). There was also no statistical association between stroke volume and aerobic fitness to either length of stay or complication rate [74].

These four relatively small studies might not have shown any significant benefit to using goal-directed fluid therapy in enhanced recovery protocols, but, possibly more importantly, again none suggested any harm in using this approach either. Perhaps more interesting is the similarities in the amounts of fluid that were administered intraoperatively between the three studies, and particularly how much smaller these values are (in not only the intervention but also the control groups) compared to similar studies conducted before enhanced recovery after surgery pathways were introduced [21].

The goal-directed protocol study by Srinivasa in 2013 was actually identical to that used in 2006 by Noblett *et al.*, where all of their patients received bowel preparation and were also fasted for longer. The total fluids given in the 2006 study were 3638 ml in the goal-directed group and 3834 ml in the control group—more than double the amount given to the control (restrictive) group in the study by Srinivasa (2013), with an enhanced recovery protocol. Unlike the 2013 study, the patients of Noblett *et al*. were also much more fluid-responsive as surgery started, and their cardiac indexes increased significantly throughout the operation (from average 3.2 l/min to 3.8 l/min) in response to filling. Overall, the complications (2% vs 15%, $p = 0.04$) and average lengths of stay (7 days vs 9 days, $p = 0.005$) in the 2006 goal-directed group were significantly lower than the liberally treated controls. Together, these results really highlight the significant impact enhanced recovery pathways have had on surgical outcomes in just an 8-year period and emphasizes the importance perioperative fluid management plays in this improvement [21, 72, 75].

Some of these results might suggest that with the increased uptake of enhanced recovery protocols, goal directed fluid therapy is no longer needed in theatres. However, the 2018 FEDORA trial still showed significantly fewer post-operative complications and shorter hospital length of stay in patients receiving goal directed fluid therapy rather than standard (enhanced recovery type) care alone [76]. In 2014, a large multicenter randomized control trial, Optimisation of Cardiovascular

Management to Improve Surgical Outcome (OPTIMISE), conducted by Pearse *et al.*, reported on the effect of using goal-directed fluid therapy together with an inotrope (dopexamine) on high-risk patients undergoing major abdominal surgery during and up to 6 h after the procedure [77]. All 734 patients followed some form of enhanced recovery protocol, making it the largest goal-directed fluid therapy trial in enhanced recovery to date. Their primary outcome was a composite score of predefined moderate or major postoperative complications and mortality at 30 days. Again, the intervention arm failed to show a significant reduction in the combined morbidity and mortality outcome, but in this larger study there was a clear trend toward benefit with the intervention (intervention group rate 36.6% vs control group rate 43.4%, $p = 0.07$, 95% confidence interval 0.71–1.01). Interestingly, for the first time the OPTIMISE study also suggested a trend toward a lower mortality at 180 days through using a goal-directed approach, although again this was not statistically significant (180 day mortality rates of 7.7% with intervention compared to 11.6% in control, $p = 0.08$). The trial had been powered to recruit more than 1000 patients, and had this initial target been reached, then maybe these two end points would have reached significance, but that remains unknown [77].

The OPTIMISE authors went on to update the earlier 2012 Cochrane systematic review with their new results as well as seven other smaller trials that had been published in the intervening period, taking the total number of studies reviewed up to 38. This new meta-analysis showed that using a cardiac output-directed hemodynamic therapy algorithm (goal-directed fluid therapy) did significantly reduce complication rates in surgical patients [77].

It is still difficult to draw definite conclusions from these findings however. Using a single composite mortality and morbidity outcome might have limited the significance of the results given that no previous study has shown a significant difference in mortality to date. It also remains unclear whether the main benefit was from using a goal-directed approach to fluid administration, inotropic support, or both (OPTIMISE is one of the first studies to combine this approach in the intervention arm). And finally, although this study significantly improves the quality of the data in the updated Cochrane meta-analysis, most of the other studies in this review remain small single-center studies reporting their outcomes in different ways. Many of these studies are also more than 10 years old now and predate enhanced recovery pathways [77].

Ultimately though, goal-directed therapy has repeatedly been shown to be a safe intervention. Better fluid management through enhanced recovery pathways or through goal-directed approaches has both been shown to independently reduce postoperative complications. A goal-directed fluid approach may also add extra benefit to enhanced recovery protocols, particularly in higher risk patients, although this will require a large and well-powered clinical trial to answer conclusively [21, 74, 77, 78]. Two such trials are currently recruiting across the UK, Optimisation of Perioperative Cardiovascular Management to Improve Surgical Outcome 2 (OPTIMISE 2), and the ‘Fluid Optimisation in Emergency Laparotomy (FLOELA) trial, looking at patients undergoing elective and emergency major-abdominal surgery respectively [79].

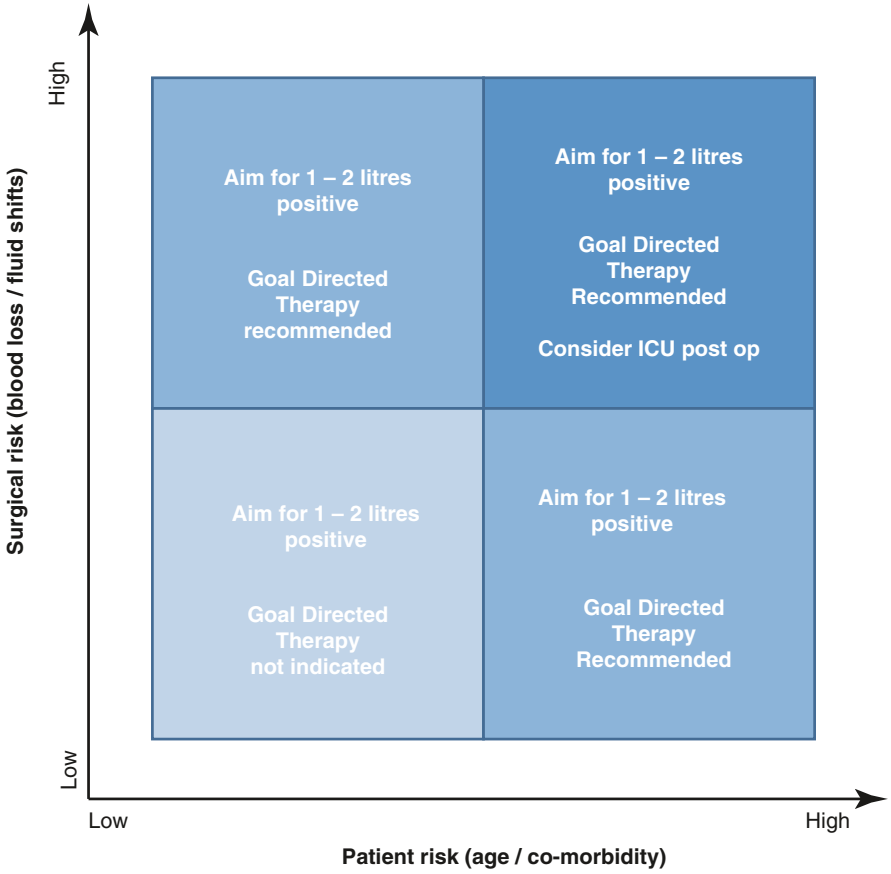

Fig. 15.4 The fluid management approach used should depend on both patient and surgical risk factors, with goal-directed fluid therapy (GDFT) indicated in higher risk cases (Adapted from [27])

For now, the biggest benefit to using a goal-directed approach is almost certainly in patients whose preoperative fluid status has not been optimized successfully and will start surgery fluid-responsive. As it is difficult to predict which patients will fall into this group, one suggestion is to use goal-directed therapy in all patients to ensure those patients that would benefit from goal-directed fluid therapy will still receive it [21]. In certain operations where large amounts of blood loss or significant intercompartmental fluid shifts are to be expected, it seems logical that targeting fluid therapy based on cardiac output monitoring should be seen as best practice [62].

Currently, consensus UK guidelines recommend using an individualized fluid plan in *all* enhanced recovery patients. They also emphasize that some patients will benefit from cardiac output optimization through a goal-directed approach, with higher risk patients having higher risk operations most likely to gain [16, 21]. See Fig. 15.4 [27]. The UK Enhanced Recovery Consensus statement specifically

recommends the use of intraoperative fluid management technology (such as the esophageal Doppler) in any operation, with any of the following features [16]:

- Major surgery with a 30-day mortality rate of >1%
- Major surgery with anticipated blood loss of >500 ml
- Major intra-abdominal surgery
- Intermediate surgery (30-day mortality >0.5%) in high-risk patients (e.g., age > 80, history of left ventricular failure or previous ischemic heart disease or stroke)
- Unexpected blood loss requiring >2 l of fluid replacement
- Patients with evidence of ongoing hypovolemia or tissue hypoperfusion (e.g., persistent lactic acidosis)

Fluid Choice

Choosing which intravenous fluid to use is also vitally important to a successful enhanced recovery pathway. In general, all intravenous fluids fall into one of just three categories:

1. Crystalloids
2. Colloids
3. Blood products

Crystalloid solutions are mixed with electrolyte or glucose ions; for example, water is mixed with sodium chloride ions to make up saline solutions. They are best used to replace insensible losses (which are often mixed with electrolyte disturbances; e.g., sweating causes salt and water loss). Some can also be used as resuscitation fluids as they will also influence hemodynamic status—the exceptions are dextrose-based solutions as cellular glucose uptake is so rapid that no significant hemodynamic effect is seen. Crystalloids can be classified based on their constituent ions and their osmolality; see examples in Table 15.2 [22, 42, 80].

Colloid solutions, on the other hand, are solutions mixed with macromolecular solutes instead of electrolyte ions. Examples include starch, gelatin, or dextran solutions. These solutes exert an osmotic pressure across the glycocalyx endothelial wall and due to their particle size are thought to remain inside the intravascular space longer (and therefore exert a long-lasting hemodynamic effect) than crystalloid solutions [22, 42].

Blood products consist of individual blood constituents such as red cells, platelets, fresh frozen plasma (FFP), or clotting factor mixes.

Which fluid type is the "best type" of fluid remains hotly debated. Ideally, fluid losses should be replaced with fluids with a similar composition in an aim to keep physiological normality [22]. For example, blood loss should be replaced with blood products wherever possible, such as packed red cells as well as with platelets and other clotting factors if the blood loss is significant.

Table 15.2 Examples and constituents of different crystalloid solutions

Fluid	Osmolality (mOsm/l)	pH	Dextrose (g/dl)	Na^+ (mEq/l)	K^+ (mEq/l)	Ca^{++} (mEq/l)	Lactate (mEq/l)	Cl^- (mEq/l)	Acetate (mEq/l)
Plasma	285–295	7.4	4–7	142	4	5	27	1	
0.9% saline	308	5.5		154				154	
Hartmann's	279	6.5		131	5	4	29	111	
5% dextrose	278	4.0	5						
0.18% saline/4% dextrose	283	4.0	4	30				30	
Plasma-Lyte	294	7.4		140	5			98	27

Adapted from [22, 42, 80]

Insensible losses (such as through perspiration and respiration) should be replaced with balanced crystalloid solutions, and 0.9% saline solutions (including some colloids that are mixed with 0.9% solutions) should be avoided wherever possible. There are very few studies that show their administration to result in clinical benefit, and they have frequently been shown to cause a hyperchloremic acidosis through excess sodium and chloride administration, which may in itself be harmful [21]. Plus, in 2018 two large trials (over 20,000 patients total) reported 0.9% saline use was associated with significantly higher rates of major adverse kidney events when used in both the emergency department and in critical care settings, and 30 day in hospital mortality was also higher in critical care with saline use (10.3% va 11.1%, p = 0.06) [81, 82]. However, while Hartmann's is a balanced crystalloid solution, simply repeatedly giving Hartmann's alone will still result in an exceptionally high sodium load and a potassium shortage [18].

The British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients (GIFTASUP) advise that patients receive the following to meet their minimum daily maintenance requirements [80]:

- 1–2 mmol/kg of sodium
- 1 mmol/kg of potassium
- 30 ml/kg water

Consequently, maintenance fluid regimes should aim to replace the above, and ideally at a rate of less than 2 ml/kg/h (including any drug infusions) according to the consensus statement from the British Enhanced Recovery Partnership [16, 80]. Where intravenous fluids do need to be continued postoperatively, these guidelines strongly recommend using a low-sodium crystalloid solution (e.g., 0.18% sodium/4% dextrose with potassium) to minimize the risk of developing postoperative ileus from excessive sodium administration [16, 21].

In terms of replacing other volume losses, most goal-directed fluid studies have used colloid boluses. This is because colloid boluses are thought to increase stroke volume and blood pressure more (and also more quickly) than the same volume of a crystalloid solution, due to colloids being less likely to leak across the glycocalyx and out of intravascular space as rapidly as crystalloid solutions [21, 22].

The Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial (a large, multicenter randomized control trial comparing crystalloids and colloids for resuscitation of hypovolemic shock) showed a significant reduction in 90-day mortality in the colloid group, suggesting benefit in using colloid boluses in fluid-responsive patients to replace volume loss [83]. However, at least two other large randomized trials have shown that using starch-based fluids in critical care patients is associated with an increased risk of kidney injury or the need for renal replacement therapy, throwing this perceived survival benefit into question [84, 85].

However, both of these trials specifically looked at critically ill patients and many of whom had already been fluid-resuscitated prior to randomization. There is no evidence in the literature currently to suggest that using starch solutions perioperatively in surgical patients to treat a blood volume deficit increases the risk of adverse renal events [86]. Perioperative patients, who are normally fit and well at the start of surgery, constitute a very different physiological cohort to shocked patients on intensive care, and it may be that this extra risk of renal damage is due to damage to the glycocalyx as a result of the systemic inflammatory changes seen in shock [21]. In perioperative patients with preexisting renal impairment, however, it is probably still sensible to avoid using synthetic colloid solutions, and again the decision of whether to use crystalloid or colloid solutions will need to be made on a case-by-case basis as part of each individualized fluid plan [21].

Conclusion

Enhanced recovery pathways offer significant benefits to patients in terms of reducing morbidity and also length of stay after elective surgery; they are gradually being used in more and more surgical specialties and increasingly becoming standard perioperative care [15]. Rather than suggesting radical new treatments, enhanced recovery methodology emphasizes and focuses around doing simple things well, and its success is principally focused on aiming to maintain "physiological normality" as much as possible perioperatively [3]. Fluid management is a central component to the success of this approach, and the focus should be to achieve an appropriate individualised approach throughout the perioperative period [21]. Intraoperatively this is likely to mean aiming for a moderately liberal fluid balance and finishing major surgery 1–2 litres positive overall [27]. Minimizing preoperative dehydration through shortening fasting times and avoiding mechanical bowel preparation is as important to this process as encouraging oral intake and avoiding excessive intravenous crystalloid administration postoperatively [21]. Good clinical assessment is essential throughout this process, and intraoperatively, this should focus on using dynamic markers where possible, and a goal-directed approach targeting increased cardiac output is recommended in all high-risk patients and major surgical cases [16, 45]. Losses should be replaced with similar fluids, and fluid challenges are a particularly useful tool for the anesthetist in assessing a patient's fluid responsiveness [42]. Ultimately, the approach to giving fluids should be considered the same

as the approach with any other pharmacological drug—they should be given at the correct time and in the correct dose, only given when indicated, and due care must be paid to the potential adverse effects they can cause in overdose [87].

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Venous Circulation: A Few Challenging Concepts in Goal-Directed Hemodynamic Therapy (GDHT)

16

Simon Gelman, Leroy D. Vandam, and G. Benjamin

Abstract

A decrease in circulating blood volume means a decrease in stressed volume (Vs). Any vasodilation (veno-dilation), iatrogenic (i.e. spinal or epidural anesthesia) or resulting from pathologic processes (e.g., sepsis), might lead to an increase in unstressed volume (Vu) and a decrease in Vs. There are two ways to increase Vs. One is to infuse fluid. If the infused fluid does not exert transmural pressure (Ptm) above 0, it is still Vu. This might be the reason for the lack of fluid responsiveness. When/if infused fluid increases Ptm above zero, this would increase Ptm, increasing BP and/or CO. The second way to increase Vs is to administer a small dose of a vasopressor to constrict veins, decrease venous capacity, squeeze blood out of compliant veins, and increase Vs. Combining an alpha-1 adrenergic agonist with a beta-2 adrenergic agonist might be useful, because that would speed up the conversion of Vu to Vs (mainly within the splanchnic system). Therefore, if small doses increase BP and/or CO, it is reasonable to assume that this was the result of conversion of part of the Vu into Vs. This might have the benefit of preventing excessive fluid load.

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Background and Basic Concepts

Many events occur between a surgical intervention and its outcome. The physiologic mechanisms that underlie these events are not well understood or sometimes even known; let us refer to them as a "black box." Actually, they do not constitute a box, but instead a large building with many floors and many rooms on each floor. Here I will be opening a door to only one room, talking about only one form of drug, a fluid infusion. Moreover, I will be discussing only the volume of the fluid, not its composition, nor specific clinical conditions such as shock, nor techniques for measuring and monitoring hemodynamic variables, unless such techniques have relevance to physiologic aspect of goal-directed hemodynamic therapy (GDHT). Some details of the physiologic function of the venous system not directly related to GDHT are not addressed in this chapter but are available elsewhere [1–3]. Thus, in this chapter we will concentrate on the function of the venous system related to GDHT.

Over the last four decades, we have lived with the relatively well-justified and partially supported hypothesis that one of the main ways to achieve good outcomes after surgical interventions is to assure adequate blood flow to tissues [3–5]. The Starling law says that the more strongly the cardiac chamber walls are stretched, the stronger the myocardial contractions that follow [6]. This principle was the physiologic basis for the hypothesis that an increase in fluid infusion (and therefore an increase in volume) should increase cardiac output (CO) and improve the wellbeing of patients undergoing surgical interventions, the approach referred to as goal-directed hemodynamic therapy (GDHT). Recent review and thoughtful analysis of available data on more than 12,000 cases has elicited many controversial observations and forced the authors to conclude that, despite some clear successes of GDHT, "…the most effective GDHT strategy remains unclear" [7].

To a large extent, the purpose of GDHT is to achieve and maintain adequate CO [8–10]. However, the outcomes associated with GDHT have been inconsistent. Many studies demonstrated the benefits of GDHT in terms of perioperative morbidity, mortality, and length of stay in intensive care units (ICUs) and hospitals [11, 12]; while other studies failed to show any serious advantages [7, 13–18].

Generally, CO should be adequate to maintain indicators of adequate metabolism within normal values. Those indicators include pH of the blood and/or tissues, lactic acid concentration in the blood, the oxygen saturation of arterial and venous blood, among many others. In this chapter we will focus on the adequacy of hemodynamics, namely stroke volume (SV) and CO.

A few definitions are needed before this discussion.

Definitions and their Physiologic Meanings

There are **intramural, extramural, and transmural pressures** (Pim, Pem, and Ptm, respectively). Intramural or intravascular pressure is a pressure within a vein, measured by introduction of tubing or a needle. Pem, or extramural pressure, is

assumed to be zero in the majority of publications [3, 19]. However, in reality Pem is complex and might vary significantly from zero; for example, it can be dramatically elevated during inflammation [20–22].

Transmural (or distending) pressure (Ptm) is the difference between the Pim and Pem. Here, the literature can be confusing: often Pem is assumed to be zero. On the one hand, we know that Pem often is not zero; this would lead to inaccurate calculation of Ptm. However, Ptm is quite important, because it is considered by many to be the driving pressure for venous flow [1, 3]; when Ptm is above zero, there is flow within the vein. If Ptm equals zero, there is no blood flow [1].

Mean Circulatory Filling Pressure (MCFP) is the pressure within the entire vasculature during cardiac arrest; pressure is the same in all arteries and veins because blood is not moving [23, 24]. The MCFP is usually between 7 and 12 mm Hg. The similar term **Mean Systemic Filling Pressure (Pmcf)** is also often used. This is the pressure measured in certain vascular beds when arterial and venous flow are simultaneously interrupted [19].

There has been serious controversy over the importance of this variable (MCFP or Pmsf)). Starting with Guyton in the 1950s, many prominent physiologists have considered this pressure to be central to the venous system and the driving force for venous return (VR), and numerous experiments support that position [3, 23]. On the other hand, quite a few researchers have suggested that the MCFP is not the driving force behind the VR, asserting instead that the force that remains from the left ventricle contractions after passing the capillary bed drives the VR [25–27]. Thus, in the latter view, the MCFP is the Ptm at a certain level (at a certain generation) of the venous system.

Venous capacity is the volume of blood within a vein (or the entire venous system) at a certain distending pressure (Ptm).

Compliance. While venous capacity describes the relationship between volume and pressure (V/P) at one point (the volume at a certain distending pressure—Ptm), compliance describes the **change** in pressure per **change** in volume, graphically represented as a slope (Fig. 16.1). Thus, the capacity is a point, while compliance is a slope**.**

Venous capacitance describes the overall continuous relationship between volume and distending pressure. Rothe says that "vascular capacitance describes the overall V/P relationship whereas compliance, capacity, stress volume, and unstressed volume are subsets of capacitance" [19]. Many authors use the terms capacitance and capacity interchangeably.

Unstressed volume (Vu) is the volume of blood in a vein when transmural, distending pressure (Ptm) equals zero. In experiments and even in the clinical setting, Vu is determined by taking a few pressure measurements when the volume within a vein is changed. A line is drawn through those measurements on a graph and extrapolated to zero pressure (Fig. 16.1); the value at the intersection of the line with the X-axis is the Vu. In the clinical setting a similar approach relies on plotting different levels of positive end-expiratory pressure (PEEP); again a line is drawn through those points and extrapolated to zero pressure. This approach is sometimes called inspiratory hold [28, 29].

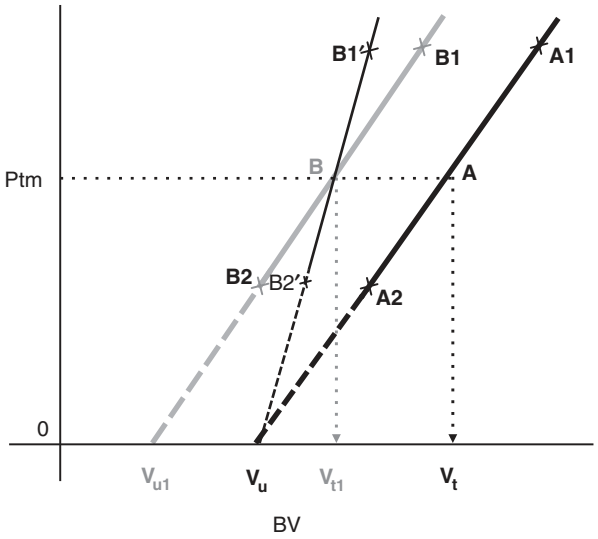

Fig. 16.1 Determination of venous compliance, capacity, stressed and unstressed volumes. BV - blood volume; C - compliance; Ptm - transmural pressure; Vu and Vs - unstressed and stressed volumes, respectively. The plot depicts the relationship between BV and Ptm. Point A represents BV in the vein (Vt) at a certain Ptm. Points A1 and A2 represent values of Vt observed during temporary partial occlusion of the vein at different points and different degrees of occlusion. The line drawn through points A1 and A2 is a compliance line; when extrapolated to zero Ptm, the point on the X-axis is the unstressed volume (Vu). The difference between Vt and Vu is the stressed volume (Vs). If some volume of blood is withdrawn from the vein, point A moves to the left to point B. Then, points B1 and B2 are obtained using the same technique as for points A1 and A2, and a new compliance line (thick gray line) is drawn. When the new compliance line is extrapolated to zero Ptm, the point on the X-axis is a new value of Vu, the Vu1. The slopes of the two lines (thick black and thick gray) are identical, indicating that venous compliance did not change, and the decrease in Vu and Vt was associated with a decrease in venous capacity. The withdrawal of blood during different conditions may move point A to the same point B. Partial occlusions of the vein are repeated, points B1' and B2' are identified, and the new compliance line (thin black line) is built. The volume within the vein is at the same point B, but the new compliance line has a steeper slope, indicating that venous compliance has decreased. Thus, the blood volume can be mobilized from a vein or a venous reservoir by two different mechanisms, namely by a decrease in capacity (first mechanism) or a decrease in compliance (second mechanism). These two mechanisms may work in concert. *The figure is reproduced from the article by Gelman and Bigatello, Can J of Anesth, 65:294–308, 2018, with permission*

Stressed volume (Vs) is the volume when the Ptm is above zero and is considered a driving force for venous flow. It is important to keep in mind that Vs is volume moving along the veins/venous system, while Vu is blood volume without any flow. The normal ratio of Vu to Vs ranges from 30% to 70% [1–3]. Under normal conditions blood loss of 10–12% of Vt is compensated for easily without any hemodynamic changes through a few mechanisms, mainly venous constriction and shifting blood volume from compliant veins into the systemic circulation; in other words, converting part of Vu into Vs [2].

However, during different pathologic conditions, ratios can change, in either direction and to varying degrees. For example, during moderate hemorrhage the ratio Vu/Vs can decrease, while during sepsis, liver failure, or vasodilating therapy it increases dramatically. The relationships between Vu and Vs are depicted in Fig. 16.2. It is important to keep in mind that Vu and Vs are useful concepts rather than real, directly measurable variables. There is no membrane separating these two volumes. The same blood, the same red cells, may be under Vs one moment and may convert to Vu the next, and vice versa.

Vascular Resistance is usually calculated as the difference between upstream and downstream pressures divided by flow through the vessel. Thus, Ra = (Pu – Pd)/F, where Ra is arterial resistance, Pu and Pd are upstream and downstream pressures (respectively), and F is the flow through the vessel. This equation has been applied to systemic hemodynamics as well to the arterial system. Later it was applied to the venous system, initially without considering the specific characteristics of the venous wall and the venous system in general. Physiologists have made remarkable

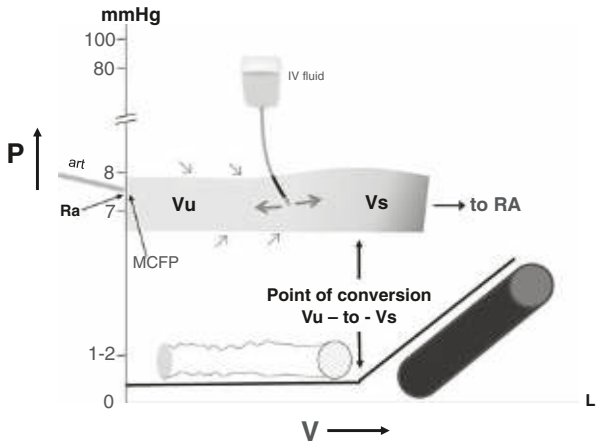

Fig. 16.2 Model of the venous circulation as a single vein. P (mmHg) - transmural, distending pressure; *V* - venous blood volume; *Vs* and *Vu* - stressed and unstressed venous volumes, respectively; *Ra* - arterial resistance; *RA* - right atrium; *MCFP* - Mean Circulatory Filling Pressure; multiple small arrows outside of venous wall—veins entering the large single vein/entire venous system. **Upper part of the schema** illustrates an increase in volume and pressure within the vein during fluid infusion. Volume from intravenous fluid as well as from upstream portions of the vein moves downstream without stretching venous walls, hence without generating P or flow. This is Vu (light shade), about 70% of the V under normal circumstances. As inflow progresses, stretch of the vessel walls generates P and flow; this is Vs (dark shade), about 30% of the venous V. The point of volume at which P starts to increase above zero may be called point of conversion of Vu-to-Vs. **Lower part of the schema** illustrates an increase in P during fluid infusion prior to and beyond the point of Vu-to-Vs conversion. The narrow oval left end of the horizontal tube (vessel) and zig-zag walls of the tube symbolize the wall of the vein that has V = 0. The round right end of the tube at the point of conversion of Vu-to-Vs symbolizes the completely open vein by blood within the vein under $P = 0$. Further increase is volume would lead to increase in $P > 0$ and conversion of Vu to Vs. The author is thankful to Dr. Luca Bigatello for participating in the design of the figure

progress in understanding the function of the veins, while average physicians too often ignore some clinically important characteristics of the veins and the venous system overall.

We often equate vascular resistance with vasoconstriction. Where arteries are concerned, this is correct in the majority of situations, but is often misleading when applied to the venous system. An increase in vascular tone (vasoconstriction) in arteries is usually associated with greater impedance to flow, decreased flow, and increased calculated vascular resistance. On the other hand, the constriction of veins, particularly compliant veins, does not increase the impedance to the flow greatly, but it shifts the blood volume from compliant veins downstream towards the heart.

Thus, the constriction of arteries is associated with decreased flow to tissues and a decrease in CO, while constriction of veins may be associated with an increase in both VR and CO [1, 2, 30] (please also see the sub-section below entitled "two-compartment model," and Fig. 16.3).

Elasticity is springiness, the capability of a strained body to recover its size and shape after being squeezed or stretched. In terms of the vasculature, it describes the vascular wall that stretches when an aliquot of blood enters a segment of the vessel. Then the wall recoils, pushing the aliquot downstream [3, 31].

Sheldon Magder correctly concludes his excellent review: "The circulation starts with a potential energy which is due to the stretching of the elastic walls…by volume it contains even when there is no blood flow." [3].

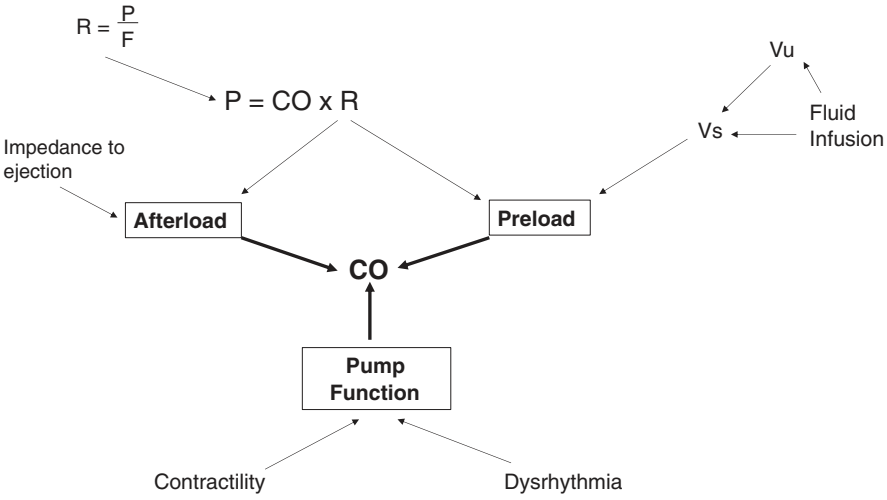

Fig. 16.3 Schema of Cardiac Output Regulation. Cardiac Output is determined by function of 3 components: preload, pump function of the heart and afterload. There are quite a few variables that affect cardiac function via these three components *CO* cardiac output; *Vu* and *Vs* unstressed and stressed volume, respectively; *R* resistance; *P* arterial pressure

The two-compartment model divides the vasculature into a fast compartment (with higher velocity of flow) and a slow compartment. This model was described in 1912 by the Dutch physiologist August Krogh [2, 32] (Fig. 16.3).

The fast compartment starts at the aorta: the blood flows from the left ventricle through the aorta and arteries, enters the capillaries, and then flows through the venules, veins, large veins, and finally enters the right atrium. The veins in the fast compartment are usually less compliant than those in the slow compartment. The latter starts with coeliac and mesenteric arteries that branch from the aorta; the blood flows through these arteries, splanchnic organs and tissues (stomach, intestines, pancreas, spleen, liver), then through the hepatic veins, finally entering the inferior caval vein. The much greater compliance of the veins in the slow compartment compared with those in the fast compartment means they have very different responses to similar stimuli (Fig. 16.4).

The most important difference between the two compartments is that the constriction within coeliac and mesenteric arteries is associated with a decrease in flow into the slow compartment. This decreases the pressure and volume within the compliant splanchnic veins and their recoil. This in turn shifts the blood volume downstream to the systemic circulation and is reflected in an increase in VR and CO (Figs. 16.3 and 16.4). On the other hand, constriction of arteries feeding the tissues

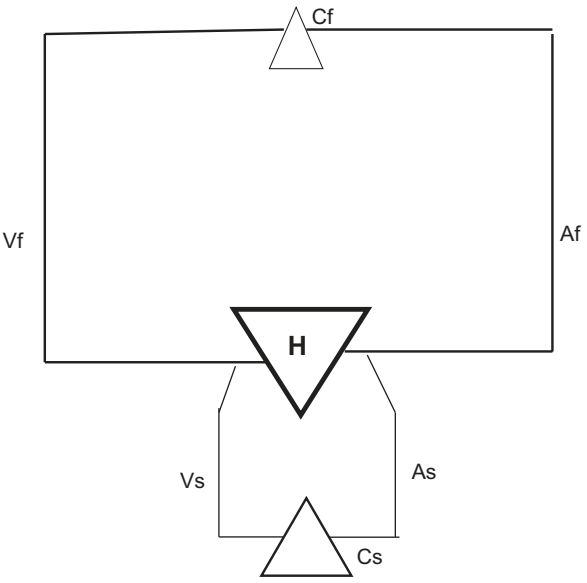

Fig. 16.4 Two-compartment model. Af and As—Arteries in the fast and slow compartments, respectively. Vf and Vs—Veins in the veins in the fast and slow compartments, respectively. Cf and Cs—capillaries within tissue of fast and slow compartment, respectively. Different sizes of Cf and Cs illustrate the differences in blood volume within the two compartments. Constriction of Af and/or Vf leads to a decrease in flow, Venous Return (VR) and Cardiac Output (CO). Constriction of As and/or Vs would lead to a decrease in venous capacity, increase in VR and CO.

within the fast compartment may lead to a decrease in flow and be associated with a decrease in VR (Figs. 16.3 and 16.4). Thus, the same insult to the arteries within the slow and fast compartments may elicit opposite overall hemodynamic effects. It is difficult to predict which of these effects will prevail. This specific issue is addressed below in the section entitled "Physiologic Effects of Some Adrenergic Drugs on the Venous System."

Thus, the vasculature in the splanchnic system are in the slow compartment, while the vessels in the remaining organs and tissues are within the fast compartment.

It is important to keep in mind that conceiving of the vasculature as having fast and slow compartments may be appealing, but sometimes may not be entirely accurate. Veins are more compliant than arteries, but they are compliant to different degrees, sometimes regardless of their anatomical location. Therefore, we may consider that very-compliant veins constitute the slow compartment, and less-compliant veins represent the fast compartment, regardless of their anatomic location.

The emptying of the venous reservoir is achieved by both active and passive mechanisms [1]. The active mechanism involves an increase in sympathetic nervous system discharge that leads to venous constriction. This empties the veins and shifts the blood volume downstream to the central vasculature. A passive decrease in venous capacity results from decreased flow of blood into compliant veins. This is associated with simultaneous decrease in pressure and volume within these veins, leading to recoil of the venous wall. When inflow of blood into the veins decreases due to constriction and/or occlusion of an artery or the aorta, the venous wall recoils and blood from those veins is expelled downstream, as during active venous constriction [33, 34]. Often both active and passive mechanisms are more or less equally involved. However, depending on conditions (particularly during a pharmacologic intervention), the relationship between active (sympathetically mediated venoconstriction) and passive (recoil of the venous wall) mechanisms can affect the relationship between Vu and Vs. Many different stimuli including, for example, epidural, spinal, or even general anesthesia, may change this relationship. These and other insults unavoidably lead to an increase in Vu and an decrease in Vs, which would decrease CO. High Vu might indicate a condition of high venous compliance in which additional fluid challenge would further increase Vu, leaving Vs relatively unchanged, without any immediate hemodynamic effects. Such a situation might become the cause of a lack of fluid responsiveness.

Given normo-volemia and a normal Vu/Vs relationship, infused fluid (at least at the beginning of the infusion) may constitute Vu without any effect on Vs or hemodynemics. This may lead to overloading without any hemodynamic signals during the infusion. However, when the effect of anesthesia dissipates later, Vu will decrease, simultaneously increasing Vs. This might be associated with hypervolemia and many typical consequences of overloading such as local inflammation, tissue and pulmonary edema, and cardiac failure.

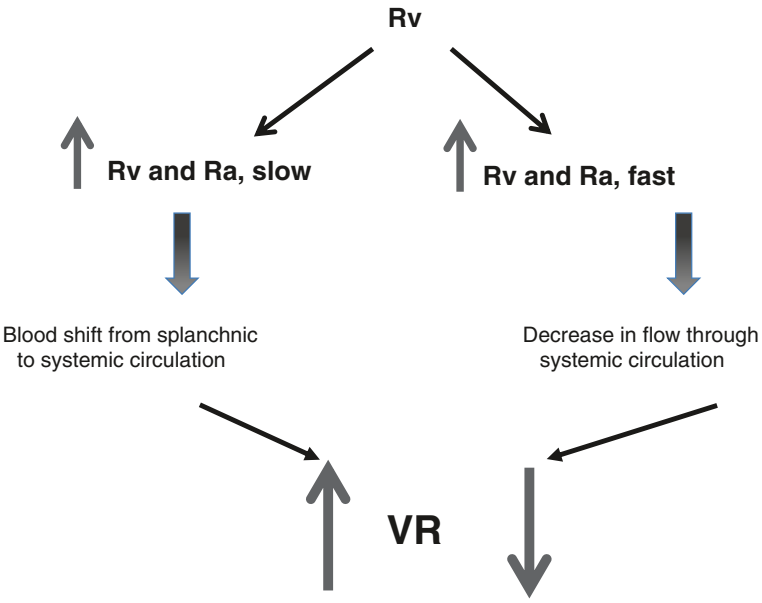

Fig. 16.5 Schematic presentation of the effects of resistances on blood flow within the two compartments. Increase in resistance in both arteries and veins in the slow compartment is associated with a shift of blood volume from that compartment to the fast compartment (systemic circulation). The increase in resistance in the fast compartment decreases the flow through the whole systemic circulation including decrease in venous return

Determinants of Cardiac Output

Since the main goal of GDHT is to maintain adequate CO, we must understand what determines the CO. Cardiac output depends on only three measured physiologic variables: preload, pump function of the heart, and afterload (Fig. 16.5).

Preload tells us how much blood is reaching the heart. It is the load to which a muscle is subjected before shortening, i.e., the state of the heart at the end of diastole, when there is maximal volume (end-diastolic volume) within the heart, which stretches the wall of the left ventricle and leads to ventricular contraction and ejection of the blood into the aorta and arterial system. In other words, preload is the maximal end-diastolic ventricular volume and maximal end-diastolic ventricular pressure that stretches the ventricular wall. The more the left ventricle stretches from the volume of the blood within the chamber, the stronger the resultant contraction of the myocardium, provided adequate pump function of the heart.

Pump function of the heart mainly refers to myocardial contractility, i.e., the ability of the ventricle to contract and eject the maximal possible amount of blood into the aorta. However, contractility is not the only determinant of heart pump function. Conditions that might lead to cardiac insufficiency include certain dysrhythmias as well as any other intracardiac factors that decrease ejection and SV.

Afterload is the resistance of the overall circulatory system against which the left ventricle pumps blood. The impedance to ejection can come from many different extracardiac factors, including but not limited to aortic stenosis and increased intrathoracic pressure [35, 36].

Also, afterload distributes the CO among different tissues and organs depending on their needs by changing the degree of constriction of arteries and arterioles.

Clinically, it is often assumed that calculated vascular resistance is an indicator of afterload. However, mean arterial pressure might reflect afterload even more accurately [30], partially because resistance is calculated from values for pressure and flow, while arterial pressure is directly measured and is in itself a determinant of afterload (Fig. 16.5).

Physiologic Basis for GDHT and Fluid Responsiveness

GDHT is focused on achieving adequate SV and CO, which obviously implies measurement of both parameters. Depending on those values, and supported by other indicators of adequacy of tissue perfusion, it is decided whether additional fluid volume needs to be administered. Starling's Law is the basis for this approach. A higher volume of fluid within the left ventricle would stretch myocardial fibers, increasing the strength of the following contraction of the myocardium, thereby increasing SV [3, 5, 6].

Fluid responsiveness is an increase in SV and CO in response to an infusion of a relatively small amount of fluid. Fluid responsiveness is usually assessed to justify the decision to infuse additional fluid or not. SV/CO is measured before and after infusion of 200–300 ml of crystalloid (or half of that amount of a colloid). Such an approach has strong support [37, 38]. If that amount of fluid increases CO by at least 10%, the decision to infuse additional fluid seems justified. Thus, ideally, we would infuse fluid as long as it continues to increase CO and would stop the infusion when CO stops increasing. At that point other options (e.g., pharmacologic interventions) to address arterial hypotension or other signs of deteriorations in the patient's well-being should be considered.

However, it turns out that only about half of patients undergoing the GDHT demonstrate such fluid responsiveness [39, 40]. Does lack of responsiveness to fluid challenge indicate no need for additional fluid infusion? To answer this question, we need to consider other physiologic and clinical reasons for this absence of fluid responsiveness [30] (Box 16.1).

Box 16.1 Conditions that may lead to lack of fluid responsiveness

- Insufficient pump function of the heart
- Hypovolemia
- High Vu/Vs ratio
  - Vasodilation
  - High venous, vascular, pulmonary, chest compliance

Failure to respond to a small fluid challenge might be due to a significant degree of hypovolemia, which prevents such a challenge from achieving even a temporary increase in blood pressure and/or SV and CO [30] (Box 16.1).

Another possible cause of decreased fluid responsiveness is high pulmonary and/or chest compliance.

Insufficiency of cardiac pump function is another reason for absence of response to the fluid challenge. If this is the case, the fluid challenge might even decrease arterial pressure and/or SV and CO. Many conditions can diminish pump function (Fig. 16.5), including a decrease in myocardial contractility, dysrhythmias, compression of the heart and/or large vessels by cardiac tamponade, increased intrathoracic pressure (including pneumo- or hemo-thorax), and others. Insufficient myocardial contractility might be reflected in the position of the patient's heart at the right end of a Starling curve. In that situation, additional fluid infusion would actually aggravate the patient's condition by further depressing cardiac pump function.

Any vasodilation, iatrogenic or pathologic, is usually reflected in increased venous capacity and/or compliance. This also may be associated with lack of fluid responsiveness.

It has been recently suggested that one of many possible reasons for a lack of increase in CO after fluid challenge is an unfavorable ratio of Vu to Vs within the venous system [30].

It is easy to misinterpret a lack of fluid responsiveness. For example, when the infused fluid ends up in the Vu (prior to the point of Vu-to-Vs conversion, Fig. 16.2), the infused fluid will not affect the hemodynamics at all. The more compliant the veins, the more likely such a situation. Continuous infusion could then overload the Vu, convert a part of Vu into Vs, eventually leading to overloading. It is not surprising that GDHT is sometimes associated with poor outcomes.

If a fluid infusion (increasing preload) is being considered for the treatment of a patient with arterial hypotension and/or inadequate CO, it is important to keep in mind the possible physiologic effects of such a measure.

Preload is determined by Vs in the vasculature, and Vu represents the reservoir. Though Vu is normally about 70% of the total blood volume, a severe or even mild inflammatory response to surgical intervention could dilate the venous vasculature and increase Vu [41]. Anesthesia, particularly spinal or epidural, dilates veins and increases Vu. On the other hand, during a surgical intervention, controlled ventilation (which is associated with an increase is sympathetic discharge), might decrease Vu and increase the Vs. All these factors make it difficult to predict the response of Vu/Vs during the perioperative period.

The blood in the Vu does not directly participate in hemodynamics, while the Vs blood plays a crucial role in the overall circulatory system. Infused fluid can increase both the Vu and Vs. At the beginning of the infusion, the fluid will constitute the Vu more than Vs, because Vu exerts lower pressure than Vs (by definition), and fluid would flow to the lower pressure. The new Vu (former Vu plus infused fluid) would increase until Vu-to-Vs conversion and Ptm exceeds zero (Fig. 16.2). At that point the whole volume in the vasculature, by definition, becomes Vs. Continued infusion

would further increase Vs, Ptm, and flow (Fig. 16.2). An increase or decrease in Vs and Ptm depends on many factors including the infused volume, venous tone, and compliance [1–3, 30].

Another way to increase Vs and preload is to convert a part of the Vu into Vs. Beforehand one should be relatively sure that the Vu is large enough to be decreased safely. We can achieve such a conversion by administering a veno-constrictor (see below, the section entitled "Physiologic Effects of Some Adrenergic Drugs on the Venous System").

It should now be clear that the same total blood volume may produce different ratios of Vu to Vs, and that such differences might be responsible for a lack of fluid responsiveness. Infusion of fluid, particularly small amounts, would not cause any change in hemodynamics because of high venous compliance. Such a small amount of fluid would slightly increase Vu (without any change in pressure) but would not noticeably affect Vs. That result might be mistakenly interpreted as showing no need for additional fluid infusion.

We do not yet have a fast and easy method for determining Vu and Vs. Development of such a technique is urgently needed.

The Physiologic Effects of some Adrenergic Drugs on the Venous System

This section addresses the effects of widely used adrenergic drugs such as phenylephrine (PE) and noradrenaline (NE) on the venous system (Fig. 16.6).

Phenylephrine (PE) is an alpha-1 adrenergic agonist that constricts both arteries and veins. There are more alpha-1 adrenergic receptors in the veins than in the arteries [42, 43]. Both vasculatures will be constricted in a dose-related fashion, but relatively small doses of the drug constrict veins to a much greater extent than they constrict arteries. Larger doses may lead to some additional constriction of veins, but only if the smaller dose did not elicit nearly maximal venoconstriction. Significant doses of PE constrict both arteries and veins. However, if veins are already maximally constricted by smaller doses or by a physiologic condition (e.g., severe hypovolemia), large doses of PE would not further increase venoconstriction and will constrict only arteries [44].

The constriction of arteries is usually associated with decreased arterial flow. On the other hand, constriction of veins, particularly compliant veins, leads mainly to a decrease in venous capacity (if veins are not maximally constricted at that moment), which squeezes blood out of the veins downstream towards the large veins and the heart, increasing VR. This may occur only with an appropriate dose of PE and would depend on the hemodynamics overall and specifically in the veins. In a hypovolemic patient it is quite possible that veins are already sufficiently constricted to shift blood out of the veins downstream. This physiologic response is important for survival, but if PE is used in such a situation, the effect would be mainly on the arteries.

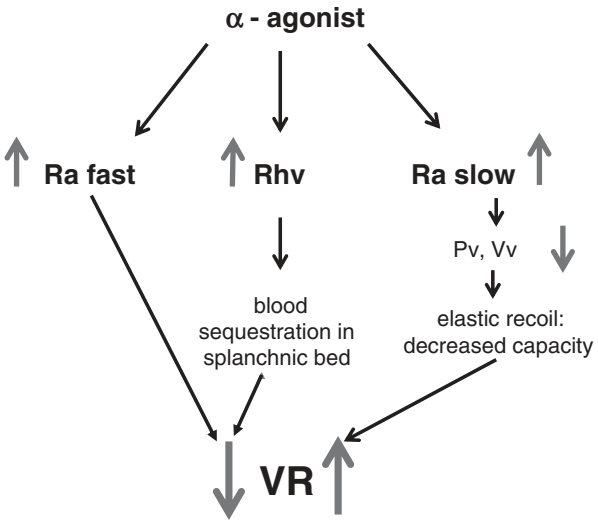

Fig. 16.6 Schematic presentation of the effects of α-adrenergic agonists on venous return. Ra fast, Rhv, and Ra slow—the arterial resistance in the fast compartment, resistance in hepatic vein and arterial resistance in the slow compartment, respectively. Pv, Vv—venous pressure and venous volume, respectively. VR—venous return and cardiac output. Arrows up and down represent the direction of change in pressure, flow or volumes. An increase in Ra fast leads to a decrease in flow through the fast compartment, including VR and CO. An Increase in Ra slow leads to a shift of blood volume from the slow to the fast compartment and increase in VR and CO.

Thus, different degrees of vasoconstriction within veins and arteries result from many factors including the dose of PE as well as the baseline initial tone of the veins and arteries.

More than 35 years ago Swedish investigators used a preparation that drained the venous return separately from other parts of the circulation. The experiments demonstrated that approximately 2/3 of the increase in arterial pressure caused by administration of PE was due to an increase in VR and only one third was from constriction of arteries [45]. The latter could severely constrict arteries, possibly decreasing flow and leading to tissue hypoxia.

However, such overall complexity is not the entire story: there is an abundance of alpha-adrenergic receptors in the hepatic veins. Activation of those receptors leads to constriction of the hepatic veins, which increases the impedance of the outflow of blood from the splanchnic system into systemic circulation. This is almost always associated with some degree of sequestration of blood within the liver [46]. This complexity in the regulation of the splanchnic circulation has led to contradictory observations. Administration of PE has been associated with a decrease [47, 48] or an increase [44, 47–60] in VR and CO.

Thus, there are data suggesting that smaller doses of PE would lead mainly to constriction of the veins and therefore an increase in VR and CO, while larger doses

could constrict not only compliant veins but also arteries and hepatic veins, decreasing both VR and CO.

Some reports confirm this notion. Administration of increasing doses of PE was associated with the following: initial small doses led to an increase in CO, while larger doses led to a decrease in CO [44, 61]. Arterial constriction leads to a decrease in flow through these arteries, but the net effect on systemic hemodynamics can vary depending on which veins these arteries are feeding. For example, arteries that supply blood to veins of relatively low compliance would lead to a decrease in flow through the whole circuit, the arteries and then veins. On the other hand, similar constriction of arteries that supply blood to very compliant veins would still be associated with decreased arterial flow, but that would also lead to decreases in pressure and volume within compliant veins, leading to their elastic recoil; the associated decrease in venous capacity results in the shift of blood volume downstream to the large veins and the heart, increasing VR and CO. We should remember that constriction of the hepatic vein can be associated with some degree of sequestration of blood within the liver and subsequent decreases in VR. In a complex clinical situation it is quite difficult to predict the result of PE administration. The best approach is likely to start with a small dose and increase it, reassessing the situation before adjusting the dose again.

Vasopressin has little effect on the venous system [62, 63]. However, it does indirectly affect both the VR and CO. In monkeys vasopressin administration produced a significant reduction in mesenteric flow without changing the CO [64]. The likely explanation is that severe arterio-constriction led to a decrease in flow through the fast compartment and CO. However, a similar constriction of arteries in the slow compartment could be associated with a decrease in inflow of blood to the splanchnic system, a decrease in pressure and volume of blood within the splanchnic veins, and a shift of blood volume downstream towards the heart with a resultant increase in VR and CO. It might be difficult to predict which of the two actions will prevail.

Beta-2 Adrenergic Agonists increase CO (Fig. 16.7). Many believe that this is due to increased myocardial contractility; in reality, the increase in contractility is more the result than the cause of the change. In normal heart function, the role of pharmacologically induced stimulation of the cardiac beta-1 receptor is minimal, if any. An isolated increase in contractility alone would increase the ejection fraction, but without an increase in preload, the change in CO would be minimal and temporary.

A series of elegant experiments performed nearly 30 years ago showed that the administration of isoproterenol, a non-selective beta-1 and beta-2 adrenergic agonist, was associated with an increase in CO. The same dose of the drug was then given in the setting of beta-1 adrenergic antagonist administration [65]. The effect of isoproterenol was the same as before. Thus, blockade of the cardiac beta-1 adrenergic receptor did not alter the effect of isoproterenol on CO. On the other hand, when the same dose of isoproterenol was given after administration of propranolol, which has non-selective beta-1 and beta-2 antagonist action, the effect of isoproterenol was significantly decreased. This means that isoproterenol increased CO not because of an increase in contractility but because of vascular effects, namely vasodilation and shift of blood volume from the splanchnic system into the systemic circulation. Contractility did increase, but mainly because of an increase in preload.

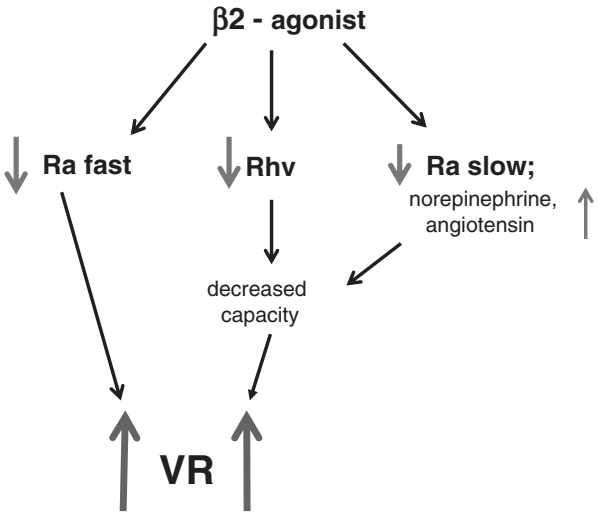

Fig. 16.7 Schematic presentation of the effects of β-2 adrenergic agonists on venous return. Ra fast - arterial resistance in fast vascular compartment (systemic circulation); Ra slow—arterial resistance in slow vascular compartment. VR—venous return and cardiac output. Arrows up and down represent the direction of change in pressure, flow or volumes. Vasodilating effects of β-2 agonists increase flow through both fast and slow compartments, venous return and cardiac output

The vasodilating effect of a beta-2 adrenergic agonist on arteries that feed veins with relatively low compliance would be associated with an increase in gradient between arterial and venous pressures and thereby would facilitate blood flow through the whole circuit. In addition, dilation of hepatic veins might facilitate the emptying of the splanchnic venous reservoir, thereby increasing VR and CO.

However, the situation turns out to be even more complex: beta-2 adrenoceptor activation is associated with increased release of norepinephrine [65, 66] and angiotensin [67–69]. These compounds constrict smooth muscle within the venous vasculature, decrease venous capacity, and increase both preload and CO. However, simultaneous constriction of the arteries in the fast compartment can decrease blood flow and flow through the whole circuit. On the other hand, constriction of highly compliant veins might facilitate their emptying into the systemic circulation, with subsequent increases in VR and CO.

Thus, usually (but not always) the increase in VR and CO, mainly due to emptying of the splanchnic venous system, prevails. As mentioned earlier, the best and safest approach would be to begin with smaller doses, observe the effect, and then decide on the next step [30].

The role of Vu and Vs. Surgical interventions are associated with the development of inflammatory syndrome to different degrees. The inflammatory response is associated with many important changes in patient's health status. Regarding hemodynamics, inflammation affects the relationship between Vu and Vs. For example, under septic conditions Vu is extremely large, and therefore attempts to counteract

hemodynamic disturbances with fluid load alone are often ineffectual and can lead to overloading.

Spinal, epidural, or even general anesthesia is often associated with vasodilation and an increase in the Vu and therefore in a decrease in the Vs. The Vs affects hemodynamics while Vu is hemodynamically mute. When anesthesia dissipates, Vu returns to normal and Vs increases. Such a situation might actually elicit quite a serious increase in Vs, reflected in clinically prominent hypervolemia [30].

On the other hand, surgical interventions are associated with sympathetic stimulation and venoconstriction. All the above factors make changes in the relationship between Vu and Vs quite unpredictable.

Infusion of fluid is likely associated with the following changes in Vu, Vs, and hemodynamics. Since Vu does not exert Ptm above zero (while Vs does), the infused volume would first mix with the Vu, where the pressure is lower. If at that moment the pressure in the vessel remains zero or below, the overall volume remains Vu. This means that hemodynamics stays exactly the same, suggesting to observers the absence of any response to fluid infusion. On the other hand, when the infused fluid raises the Ptm above zero and reaches the point of Vu-to-Vs conversion, the whole blood volume within the vessel (existing and infused) becomes the Vs, increasing flow, VR, and CO, and demonstrating fluid responsiveness (Fig. 16.2).

The higher the venous compliance, the larger the portion of the infused fluid will remain within the Vu, without the expected increase in CO. If there is any suspicion that the Vu is high and the infused fluid does not correct hemodynamics as expected, a small dose of PE might be beneficial. It would decrease Vu, increase Vs, and shed light on the clinical situation. If a small dose of vasopressor in this situation does not increase CO and/or blood pressure, thorough clinical reassessment is in order [30].

The simultaneous activation of alpha-1 and beta-2 adrenoceptors might prove useful in GDHT. This combination might provide patients with some benefit by decreasing the ratio Vu/Vs under conditions of normo-volemia. This combination of (1) constriction of compliant veins; (2) relaxation of the arterial tree; resulting in (3) decreased pressure gradient between arterial and capillary-venous vessels (which could in itself improve nutrient flow as well as VR); and (4) conversion of a portion of Vu into Vs might improve the overall results of GDHT. It seems possible that noradrenaline (NE) could serve this purpose. However, one must be careful when decreasing Vu, which does not affect hemodynamics but does serve as a reservoir when the need for an increase in Vs arises.

This hypothesis is supported by a considerable body of experimental data [1, 3–5, 8–10, 30, 41, 70–77] as well as clinical data [78].

Conclusions and Clinical Implications

- A decrease in circulating blood volume means a decrease in stressed volume (Vs). Main clinical symptoms of hypovolemia (a decrease in BP and/or CO, among others) usually result from a decrease in Vs. Given a decrease in circulating blood volume, unstressed volume (Vu) and total blood volume (Vt) can be unchanged, decreased, or even increased (for example, in some cases of cardiac

pump dysfunction or severe vasodilation, as in sepsis or during spinal, epidural, or even general anesthesia).

- Blood loss of 10–12% of Vt is usually not associated with any loss of Vs or any clinical symptoms of hypovolemia. This volume of loss is largely compensated for by conversion of part of the Vu into Vs. That prevents hemodynamic disturbances and is achieved by an increase in sympathetic discharge. Clinically noticeable hypovolemia begins when Vs starts to decrease, while Vu may already have decreased to a physiologically possible maximum.
- The perioperative period is rife with insults that affect the normal physiologic relationship between Vu and Vs. For example, any vasodilation (veno-dilation), iatrogenic or resulting from pathologic processes (e.g., sepsis), might lead to an increase in Vu and a decrease in Vs. For example, anesthesia induction of a hypovolemic patient may be associated with a catastrophic hemodynamic deterioration if pre-induction both Vu and Vs are already decreased and drugs used for induction dilate constricted compliant veins, increasing Vu and drastically decreasing Vs.
- A drastic increase in Vu might not be associated with any changes in Vs but could present hemodynamic disturbances later, when Vs would be increasing. A typical case might develop as follows: arterial hypotension during spinal or epidural anesthesia (or even general anesthesia in some cases) would dilate veins and convert a certain part of Vs into Vu. Additional fluid infusion (to compensate for the decrease in Vs) would further increase the Vu more than Vs, because Vu is under lower pressure; the infused fluid at the beginning behaves as Vu. When the hemodynamic effect of anesthesia dissipates, more of the Vu than is desirable will convert to Vs. This could constitute hypervolemia.
- There are two ways to increase Vs. The first is to infuse fluid to convert a part of the Vu into Vs. If the infused fluid does not exert transmural pressure (Ptm) above 0, it is still Vu. Even in the case of decreased Vs, initial doses of infused fluid might not raise Ptm above zero; in that case the infused fluid would behave as a part of Vu, without increasing Ptm. This might be the reason for the lack of fluid responsiveness. When/if infused fluid increases Ptm above zero (after the point of Vu-to-Vs conversion), the whole blood volume within this chamber becomes Vs (by definition) and would increase Ptm, increasing BP and/or CO (Fig. 16.2). The second way to increase Vs is to administer a small dose of a vasopressor (phenylephrine or norepinephrine) to constrict veins, decrease venous capacity, squeeze blood out of compliant veins, and increase Vs.
- Combining an alpha-1 adrenergic agonist with a beta-2 adrenergic agonist might be useful, because that would speed up the conversion of Vu to Vs (mainly within the splanchnic system). Therefore, if small doses increase BP and/or CO, it is reasonable to assume that this was the result of conversion of part of the Vu into Vs. This might have the benefit of preventing excessive fluid load.
- Lack of fluid responsiveness does not necessarily mean absence of hypovolemia. Other reasons for lack of fluid responsiveness may include insufficiency of cardiac pump function; severe hypovolemia when a small dose of fluid cannot correct the hemodynamics; high venous compliance; and/or any veno-dilation (iatrogenic or pathologic), which is a state of high Vu that would prevent the infused fluid from being converted into Vs.

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Perioperative Fluid Management in Pediatric Patients

17

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Abstract

Intravenous fluid administration is an integral part of perioperative care for children undergoing surgery. The ultimate goal of intravenous fluid therapy is to maintain cardiovascular stability, euvolemia, normal electrolyte and acid base status. The volume and composition of the replacement fluids should be based on the preoperative patient condition, type of procedure and anticipated perioperative course. Neonates and infants poorly tolerate errors in fluid and electrolyte management. The chapter will mainly focus on distinctly different pediatric physiology, advantages of optimized perioperative fasting duration and assessment of volume status in neonates and children. In this chapter, we will review the various types of fluids, newer recommendations for perioperative fluid management in children to maintain normal physiology and to improve safety and efficacy. In addition, clinical situations requiring special consideration will be narrated briefly.

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Key Points

1. Neonates and infants are more susceptible to fluid and electrolyte disturbances due to large body surface area, higher metabolic rate and structural immaturity of kidney with limited urine concentrating ability.
2. Maintenance of normal homeostasis and prevention of metabolic derangement are the fundamental goals of perioperative fluid therapy.
3. Volume and composition of the fluid therapy should be based on preoperative condition, type of procedure and anticipated perioperative course. Use of balanced isotonic solutions are recommended to avoid iatrogenic hyponatremia and hyperchloremic acidosis.

Introduction

Perioperative fluid administration is a routine practice in pediatric patients. Goals of perioperative fluid therapy are to maintain euvolemia, acid-base equilibrium and electrolyte balance. Intravenous fluids are given to replenish the preoperative fasting deficit, provide basal metabolic requirements, and replace losses from the surgical field. They also help to compensate for volume status alterations due to alterations in preload and afterload from autonomic changes during anesthesia. Mismanagement of fluid therapy can lead to serious complications and negative outcomes. Underestimation of volume loss is the most common cause of perioperative cardiac arrests in children [1].

Pediatric patients especially neonates and infants poorly tolerate any errors in fluid and electrolyte management. Their large body surface area and higher metabolic rate results in greater evaporative losses. Structural immaturity of kidneys with limited urine concentrating ability impairs regulation of extracellular fluid volume and makes them vulnerable to fluid and electrolyte imbalance. It is important to individualize fluid therapy based on the patient's condition, while giving consideration to composition, rate and duration of administration.

Body Fluid Compartments

Total body water which is the amount of sodium free water is the largest single constituent of human body. It is distributed mainly in two compartments: intracellular compartment (ICF) and extracellular compartment (ECF). Preterm and low birth weight neonates have a higher percentage of total body water (80%) as compared to adults (60%). TBW decreases with age as illustrated in the table which mainly is secondary to loss of water in ECF. Thus neonates and infants have proportionally higher fluid requirements as they have more total body water, large body surface area and increased basal metabolic rate resulting in higher fluid and electrolytes turn over (Table 17.1).

Table 17.1 Composition of the extracellular and intracellular fluid compartment

Neonate				
	Preterm	Term	Infants (upto 6 months)	Adults
ECF (%)	50	40	35–40	20
ICF (%)	30	35	35	40
TBW	80	75	70–75	60

ECF Extracellular fluid, *ICF* Intracellular fluid, *TBW* Total body weight

Table 17.2 Estimated Circulating Blood Volume

Age	Blood Volume (ml/kg)
Preterm neonate	100 ml/kg
Term newborn	90 ml/kg
Infants 3 months to 1 year	80 ml/kg
> 1 year of age	70 ml/kg

Circulating Blood Volume

Blood volume varies considerably depending on the age and size of patients. It is important to determine circulating blood volume and maximal allowable blood loss preoperatively. In preterm and low-birth-weight infants, circulating blood volume estimates as high as 100 ml/kg. Term neonates measures 90 ml/kg, as shown in the table and with increasing age and weight the circulating blood volume decreases to adult values of 70 ml/Kg [2].

Maximal allowable blood loss (MABL) can be calculated with estimated blood volume, preoperative hematocrit and the lowest acceptable hematocrit as shown below [2].

MABL = Weight (Kg) × Estimated blood volume × (Initial Hematocrit (Hi) − Lowest possible Hematocrit (Hf) / Initial Hematocrit (Hi)).

Lowest acceptable hematocrit depends on age and clinical condition of the patient as shown in the Table 17.2. For example, a term neonate weighing 4 kg coming for emergency exploratory laparotomy for necrotizing enterocolitis with a preoperative hematocrit of 36 can be expected to have circulating blood volume of 360 ml (4×90). Considering critical condition of the patient, we assume lowest acceptable hematocrit is 24 so maximal allowable blood loss is 120 ml prior to need for blood transfusion (MABL = 4 × 90× (36–24/36) = 120 ml).

Compare this to a 4 kg neonate with hypoplastic left heart syndrome undergoing repair. In this case, the child's preoperative hematocrit is around 46. Following repair the hematocrit should remain at least 40. The MABL for this baby would be 46 ml, (4 × 90 × (46–40/46) = 46 ml). Thus determining the allowable blood loss for each particular patient paying attention to preoperative factors and intraoperative concerns is crucial as there is not much room for error.

Preoperative Fasting

Preoperative fasting is imperative for children scheduled for elective surgery to minimize risk of aspiration. Recent evidence indicates prolonged fasting does not reduce risk of aspiration [3, 4]. Due to better anesthetics and improved techniques, the risk of pulmonary aspiration has decreased, and shorter preoperative fasting periods are recommended, including a lower limit of 6 h for solids, 4 h for breast milk, and 2 h for clear fluids, known as the 6–4-2-rule [4].

Subsequent clinical studies and meta-analyses found low risk of pulmonary aspiration during pediatric anesthesia and no benefit of prolonged fasting in terms of gastric volume and pH. Extended fasting can be detrimental, especially in small children. It is associated with patient discomfort, uncooperative behavior, dehydration, ketoacidosis, hypoglycemia, and hypotension after induction of anesthesia [5].

Allowing children to drink clear fluids (water, pulp free clear juices, electrolyte containing fluids, and coffee or tea without milk) up to 2 h before the procedure can increase comfort and hydration. This led to practice change in form of encouraging parents to give clears to children up to 2 h prior to the scheduled procedure. In our institution, we schedule neonates, small infants and children with diabetes or metabolic disorders as the first case of the morning to avoid unwarranted delays and associated fluid, electrolyte imbalances and metabolic derangements.

To reduce side effects associated with prolonged fasting, European Society for Paediatric Anaesthesiology, Association Paediatric Anaesthetists of Great Britain and Ireland and Society of Pediatric Anesthesia of New Zealand and Australia (SPANZA) have recently released a consensus statement advocating clear fluid intake up to 1 h before elective general anesthesia [6–8]. Early postoperative drinking and enteral feeding as desired by children is also recommended (Table 17.3).

Practice Guidelines for Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration: Application to Healthy Patients Undergoing Elective Procedures: An Updated Report by the American Society of Anesthesiologists Task Force on Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration [9].

Table 17.3 Preoperative Fasting Guidelines for Elective Procedures

Ingested Material	Minimum Fasting Period (h)
Clear liquids	2
Breast milk	4
Infant formula and non-human milk	6
Light meal [a]	6
Fried foods, fatty foods or meat	8

[a]Light meal consist of toast and clear liquids

Volume Assessment and Estimation of Fluid Deficit

Volume status and degree of dehydration can vary depending on clinical situation. It can be mild in children admitted for elective surgery, but severe in traumatized, volume depleted patients undergoing emergency procedures. Thorough clinical assessment should be done to determine the severity of dehydration. For children with known accurate recent body weight measurements, fluid deficit can be calculated based on percentage of weight lost: every 1 kg weight loss equals 1 liter of fluid deficit. Physical examination findings such as mental status, capillary refill time, presence of tears when crying, assessment of fontanelles, urine output or number of wet diapers are valuable measures to confirm degree of dehydration as shown in Table 17.4 [10, 11]. Assessment of all signs and symptoms has shown to be superior over individual findings in prediction of hypovolemia [12]. Hypovolemia can be classified into mild, moderate and severe forms based on its severity.

Mild hypovolemia is defined as 3–5% volume loss. Clinical signs and symptoms are often minimal or absent and thus the diagnosis can be missed. History of primary etiology leading to fluid losses might be the only finding. These patients have normal electrolytes and acid base status.

Moderate hypovolemia is defined as 6–9% volume loss. Apparent clinical signs are tachycardia, low normal or orthostatic hypotension, narrow pulse pressure, decreased skin turgor, dry mucous membranes, irritability, cool extremities with increased capillary refill 2–3 s (sign of decreased skin perfusion), increase in respiratory rate and sunken fontanelle. Reduction in urine output can be elicited with history of decreased number of wet diapers in a child.

Severe hypovolemia is defined as more than 10% volume loss. Circulatory instability and near shock status of a child presents with tachycardia, hypotension, parched mucous membrane, lethargy or coma, increased capillary refill of greater than 3 s with cool and mottled extremities, and deep respirations with an increase in

Table 17.4 Assessment of Dehydration

Dehydration (%)	Mild (≤ 5%)	Moderate (6–9%)	Severe (>10%)
Mental status	Normal	Listless, irritable	Lethargic or comatose
Heart rate	Normal	Increased	Increased
Systolic blood pressure	Normal	Normal or low	Low
Breathing	Normal	Normal or rapid	Deep
Eyes	Normal	Decrease tear	Sunken orbit, absent tear
Mucous membrane	Moist	Dry	Parched
Extremities	Warm	Cool	Cool, mottled, cyantotic
Capillary refill (normal<1.5 -2 s	Normal	Prolonged	Prolonged
Fontanelle	Normal	Sunken	Very sunken
Urine output	Normal	Decrease	Anuric
Estimated fluid deficit	30–50 ml/kg	50–100 ml/kg	>100 ml/kg

Modified from Falszewska et al. [10]. Diagnostic accuracy of three clinical dehydration scale: a systemic review and Steiner et al. [11]. Is this child dehydrated?

rate. Anuria over the period of hrs to day might also be evident. Lack of response to painful stimulation such as IV placement should also raise suspicion of decreased cardiac output and cerebral perfusion.

Metabolic acidosis defined as serum bicarbonate concentration less than 17 mEq/L is suggestive of moderate to severe hypovolemia [11, 13]. Lactic acidosis more than 4 meq/l is associated with poor prognosis and serial lactate levels are often measured to assess shock management. Urine sodium concentration less than 25 mEq/L is also suggestive of decreased tissue perfusion. Urine is often concentrated with osmolality in excess of 450 mOsm/kg and specific gravity more than 1.015 in moderate to severe hypovolemia. It is important to recognize this is not a reliable finding in neonates who have limited renal concentrating ability, children on diuretic therapy or with osmotic diuresis and children with diabetes insipidus.

Fluid and Electrolytes Requirements

The volume and composition of peri-operative fluid therapy is usually based on preoperative status of the patient, type of procedure and anticipated course in the operating room and recovery. It is important to choose the fluids that maintains the homeostatic milieu.

Holliday and Segar in 1950s first described a practical method for prescribing maintenance fluid therapy to account for insensible losses and urine output [14]. The authors proposed that water requirement was equivalent of energy expenditure, thus 1 ml of water is required for 1 kcal expenditure. The energy expenditure or daily caloric requirements of hospitalized patients was calculated as shown in the Table 17.5 with 4–2-1 rule. Henceforth patients weighing 0–10 kg need 100 ml/kg/day, patients weighing 11–20 Kg need 1000 ml + 50 ml/Kg/day for each kg above 10, and for patients weighing more than 20 Kg need 1500 ml and an additional 20 ml/Kg/day for each kg above 20. Thus hourly requirements are 4 ml/kg for the first 10 Kg, 2 ml/kg for the second 10 Kg and then 1 ml/kg for weight more than 20 Kg. They then analyzed the electrolyte composition of human and cow's milk and thus over the years developed the practice of using hypotonic fluids like 0.225% and 0.45% saline as maintenance fluidtherapy. It was a common practice to follow 4–2-1 rule per Holliday and Segar for fluid management in healthy patients. These

Table 17.5 Daily Caloric and Fluid Requirement Based on Body Weight

Body weight(kg)	Daily Caloric Requirement	Maintenance Fluid Requirement
0–10	100 kcal/kg	100 ml/kg/day (= 4 ml/kg/hr)
11–20	1000 kcal + 50 kcal/kg for each kg from 11–20 kg	100 ml/kg/day for first 10 kg + 50 ml/kg/day for each kg from 11–20 kg (2 ml/kg/hr)
>20 kg	1500 kcal + 20 kcal/kg for each kg over 20 kg	100 ml/kg/day for first 10 kg + 50 ml/kg/day for 11–20 kg + 1 ml/kg/hr. for each kg > 20 kg

calculations were based on several assumptions to assess basal metabolic rate. They do not hold true for acute or critically ill patients. Fever, burns, sepsis and major surgery are some of the examples of increase energy expenditure and higher fluid losses and thus require more perioperative fluids. Hypotonic fluids also cause hyponatremia as explained below.

Types of Intravenous Fluids (IVF)

Crystalloid Solutions

Crystalloid solutions are composed of water with electrolytes. Ideal intravenous fluids in terms of composition, rate and duration of administration remains unclear. Hypotonic fluids like 5% dextrose (D5) with ¼ NS and D5 with ½ NS were traditionally used during the perioperative phase. This has been criticized lately because of increasing evidence of postoperative hyponatremia defined as sodium levels <135 mEq/L. Hyponatremia occurs due to deficit in sodium in the replacement fluids and impaired ability to excrete free water.There is also evidence that high level of antidiuretic hormone (ADH), also known as vasopressin, develops during perioperative period. ADH binds to the vasopressin V2 receptor in the basolateral membrane of the collecting duct, which leads to the insertion of aquaporin-2 channels in the apical membrane and ultimately to increased water permeability and water reabsorption.The primary stimulus for ADH release is an increase in osmolality, but it can also rise due to non-osmotic stimuli like stress, pain, nausea, subclinical fluid deficit, blood loss and narcotic use and in turn worsens hyponatremia.

So far 15 out of 17 randomized prospective trials showed that hypotonic fluids are associated with higher incidence of postoperative hyponatremia [15]. A Cochrane Review published in 2014 [16] highlighted again that hypotonic fluids have a higher incidence of hyponatremia (34%) as compared to isotonic fluids (17%) with 95% CI 0.38 to 0.60). Three more meta-analyses published in the same year calculated an odds ratio of 0.18 (95% CI, 0.08–0.41) of developing severe hyponatremia with the administration of hypotonic fluids. Meta-analysis published by Wang et al. in 2014 [17] compared isotonic to hypotonic IV fluids in hospitalized children. Out of ten randomized control trials five of the included studies exclusively involved children undergoing surgery. They found that hypotonic maintenance IV fluids significantly increased risk of severe hyponatremia in both surgical and medical patients. Yang et al. found that surgical patients were more hyponatremic than non-surgical patients [18].

Saline 0.9% is still widely used to avoid the risk of hyponatremia. The composition of saline 0.9% was first described in 1890s by Jacob Hamburger. It is isotonic to human plasma but has high chloride concentration as compared to plasma (154 vs 100 mmol/l) with no bicarbonate precursor. The strong ion difference (SID) which is calculated by subtracting the total strong anion concentration (chloride and lactate) from total strong cation concentration (sodium, potassium and magnesium) in plasma is 0 for 0.9% saline versus 40 mEq/l for plasma. Large volume of normal saline infusion is thus associated with decrease in SID resulting in hyperchloremic

Table 17.6 Types and Composition of commonly used Intravenous fluids

	Osmolality	Tonicity	Na^+	Cl^-	K^+	Mg^{2+}	Ca^{2+}	Buffer[a]
Plasma	288	Reference	136–145	98–106	3.5–5	0.8–1	2.2–2.6	24
0.9% saline(NS)	308	Isotonic	154	154	0	0	0	0
Lactated ringers(LR)	278	Near isotonic	130	111	4	0	2.7	29
Hartmann's solution	278	Near isotonic	131	111	5	0	2	29
PlasmaLyte	295	Isotonic	140	98	5	1.5	0	50
5% dextrose(D5)	278	Hypotonic	0	0	0	0	0	0
Sterofundin*	309	Isotonic	140	127	4	1	2.5	29
D51/2 NS)	428	Hypotonic	77	77	0	0	0	0
D41/4 NS)	329	Hypotonic	34	34	0	0	0	0
D5 NS)	555	Near isotonic	154	154	0	0	0	0

All in mmol/l except osmolality in mOsm/kg, N/A = not available
Buffer[a] consist of bicarbonate (plasma), lactate (LR), acetate (27 mmol/l in Plasma, 24 mosm/l in Sterofundin), gluconate (23 mosm/l in PlasmaLyte) and maleate (5 mosm/l in Sterofundin)
Sterofundin* not currently available in United States

metabolic acidosis. There is growing evidence both from animal and human studies that 0.9% saline might have negative impact on renal function. Zhou et al. has shown an increased incidence and severity of AKI in rats with 0.9% saline [19]. In a cross over study of healthy volunteers with 2 liter of 0.9 saline infusion, authors demonstrated significant hyperchloremia which led to renal vasoconstriction and decreased renal cortical perfusion [20].

Buffered crystalloid solutions like Ringer's lactate, Hartmann's solution, and Plasmalyte contain near physiological chloride as shown in Table 17.6. Further addition of anions such as lactate, acetate, malate and gluconate are precursors of bicarbonate and therefore act as a physiological buffer. SID of ringer lactate is 29, of hartmann's solution is 29 and that of plasmalyte is 50 mEq/L as shown in Table 17.6. Thus these fluids better mirror the extracellular fluid compartment in the body. A large retrospective matched cohort study of adult patients undergoing open abdominal surgery showed that the rate of major postoperative complications was lower in group receiving Plasma-Lyte compared to patients who received 0.9% saline (OR 0.79, 95% CI 0.66–0.97, $P < 0.05$) [21]. The use of balanced solution was associated with lower rates of postoperative infection, renal replacement therapy, blood transfusion, and electrolyte disturbances.

Colloids Solutions

Colloids are gelatinous solutions which contain particles too large to pass through semipermeable membrane, such as the capillary bed, thus they remain in the intravascular compartment longer. Colloids also increase intravascular volume by

increasing the oncotic pressure intravascularly facilitating translocation of fluid from the extravascular, interstitial and third spaces to the vascular bed. However, if a patient has a disrupted endothelium or if the colloids make their way into the interstitial space edema can worsen due to the movement of fluid leaving the intravascular compartment. Colloids are divided into two groups: natural colloids and synthetic colloids. Their use is varied depending upon geographic location, with the United States favoring albumin and Europe using synthetic colloids [22].

Albumin is a naturally occurring colloid, is highly water soluble, and constitutes 60% of total protein in plasma. It is traditionally obtained from pooled human plasma by cold ethanol fractionation due to two unique properties: high solubility and low isoelectric point. In this process, known as the Cohn method, human plasma is heated to 60 degree Celsius and then sterilized by ultrafiltration [23]. Albumin is available in two concentrations, 5% albumin solution which is isotonic and 25% albumin which is hypotonic but hyperoncotic. The higher concentration of albumin 25% allows one to administer colloid with less salts and total volume which can be beneficial for select patient populations. Albumin administration is unlikely to cause side effects because it is a naturally occuring colloid [24]. Allergic reactions may occur, although those seen with albumin are less common than with other colloids. Disruption of the coagulation cascade may occur due to effects on platelet aggregation and activation of antithrombin III [23]. Despite these rare side effects albumin has been considered the gold standard colloid for pediatric patients.

Hydroxyethyl starch (HES), gelatins and detrans are synthetic colloids. HES are modified natural polysaccharides with modified hydroxyethyl groups making breakdown by circulating amylases difficult causing a prolonged increased intravascular oncotic pressure. Hetastarches are classified based upon their concentration, weight average mean molecular weight (MW), molar substitution (MS) and C2:C6 ratio. MS refers to the molar ratio of the total hydroxyethyl groups to total glucose units. The hydroxyethyl group at the C2 position prevents breakdown by amylases hence prolonging the colloid effect. This is important because solutions with a higher MW and MS ratio have a longer effect, but also greater incidence of side effects. Additionally a higher ratio of C2:C6 hydroxyethylation substitution also leads to a longer effect. The ideal HES would have a low MW and MS ratio to decrease side effects but a high C2:C6 to have a prolonged effect. The available HES) concentrations are 3%, 6% and 10%. The available weighted average mean molecular weights are low (< 70 kDA), medium (120–270 kDA), and high (>450 kDA). MS is categorized into low and high groups, low is 0.4–0.5 molecular ratio and high is 0.62 to 0.7. In the US the available HES solutions are Hespan (concentration 6% HES, MW 450 MS 0.7 C2/C6 ratio 4:1 in saline), Hextend (6% HES 670/0.7/4:1 with balanced electrolytes, lactate buffer and glucose), and Voluven (6% HES 130/0.4/9:1 in normal saline). The side effects most commonly seen with HES) solutions are renal impairment, pruritus, and hypocoagulation. The negative renal effects are caused by renal tubular swelling creating a hyperviscous urine leading to renal tubular obstruction and medullary ischemia. This can be prevented by using new generation HES solutions with lower MW and MS. Pruritus is thought to be due to accumulation of HES solution in the skin and may last for months following infusion. This is not amenable to available treatments, but is less commonly

seen with the newer HES solutions. The coagulation effects are thought to be due to impairment of von willebrand factor, factor VIII and platelet function [23].

Dextrans are water soluble highly branched polysaccharides produced by bacteria using sucrose substrates. Two dextran solutions are available: dextran 70 a 6% solution with a MW of 70,000 and Dextran 40 also known as low molecular weight dextran a 10% solution with a MW of 40,000. The kidneys are responsible for excretion of dextrans, the threshold for excretion is 55,000 Da. Thus Dextran 70 remains within the intravascular compartment longer than Dextran 40, about 5 to 6 h compared to 3 to 4 h [23]. The advantages of dextrans include a increased volume expansion compared to albumin and HES, and also improving microcirculation [24]. Despite the excellent colloid oncotic effect, dextrans do have some unwanted effects. The disadvantages include anaphylactic reactions, hypocoagulability, negative renal effects and interference with cross match. The anaphylactic reactions seen with dextrans are more severe than with other colloids, and are due to dextran reactive antibodies. Dextrans interfere with platelet adhesiveness, cause increased fibrinolysis which is worse with high MW dextrans and cause a von willebrand type effect [23, 24]. Dextrans can accumulate in renal tubules leading to renal plugging and is more likely to happen with renal impaired patients. Dextrans can also interfere with cross matching by coating the surface of RBCs [24].

Gelatins are polypeptides formed by the degradation of animal connective tissue, they dissolve with heat and form a gelatinous substance when cooled. There are 3 types of gelatins commercially available; however, none are available in the US because of higher incidence of hypersensitivity reactions. The available types are: succinylated or modified fluid gelatins, urea-crosslinked gelatins and oxypolygelatins [23, 24]. Gelatins have a lower oncotic effect due to a MW in the range of 30–35,000, lower than the other colloids. Additionally their effect is shorter compared to the other colloids because of rapid glomerular filtration and renal excretion, enzymatic cleavage by serum proteases, and rapid movement into the interstitial space. Like other colloids, there is a negative effect on coagulation. Advantages include its cost (least expensive of the artificial colloids), long shelf life, lack of negative renal side effects, and the fact it does not accumulate in the body [24].

Importance of Maintaining Euglycemia during Perioperative Period

Metabolic derangements from prolonged preoperative fasting for small children can cause hypoglycemia, lipolysis and ketoacidosis. Glucose is the main source of energy for the brain. Severe prolonged hypoglycemia can mediate cerebral injury and poor neurodevelopmental outcomes. Furthermore, mild hypoglycemia when combined with hypoxia and ischemia can also induce cerebral insult [25, 26]. It was routine practice to administer 5% dextrose containing fluid intraoperatively to prevent hypoglycemia in past. However, concerns were raised of deleterious effect of hyperglycemia associated with 5% dextrose administration. Hyperglycemia can induce osmotic diuresis, dehydration and electrolyte imbalance [27, 28]. It is

Table 17.7 Type and Composition of Dextrose containing Electrolyte Solution

Composition (mmol/l)	Plasma (Reference)	BS-G1	Polyionique B66	Polyionique B26
Sodium	136–145	140	120	68
Chloride	**98–106**	**118**	**108**	**95**
Potassium	3.5.5	4	4	27
Calcium	2.2–2.6	2	2.2	0
Lactate	1.5	0	20	0
Acetate	0	30	0	0
Glucose	2.78–5	55.5	50.5	277

[a]IVF with dextrose concentration less than 5% are currently not available in United States

also detrimental for the brain and increases morbidity and mortality in children [29, 30].

Hence there is evidence concluding that both hypoglycemia and hyperglycemia worsens the neurological outcome in children. Glucose infusions at a rate of 120–300 mg/kg/hr has been demonstrated to be effective in preventing hyperglycemia, lipolysis and ketoacidosis especially in infants and children [31, 32]. It is common practice in Europe to use 1–2.5% glucose infusion with isotonic solution as background infusion intraoperatively. Such IVF preparations as shown in Table 17.7 are commercially available only in Europe. Perioperative fluid therapy with these balanced salt solutions (BS) have shown to avoid both hyperchloremic acidosis [33] and hyponatremia compared to hypotonic fluid infusion [34].

BS- G1 (balanced salt solution with 1% glucose) and Polyionique B66 are use as maintenance fluid therapy (background infusion) during surgery in infants and young children in Europe.

Polyionique B26 use as maintenance fluid therapy in postoperative period in normovolemic children in Europe.

Intraoperative Fluid Management

Inhalation induction with or without premedication is common practice for infants and young children undergoing elective surgery. Intravenous catheters are usually placed following mask induction. It is prudent to deair IVF tubing to avoid accidental air injection. Positive pressure ventilation during general anesthesia may promote right to left shunt across patent foramen ovale which is present in 50% of children less than 5 years and 20–25% of adult population. It is prudent to avoid accidental volume infusion in neonates and small children. This can be accomplished by either removing the excess amount of fluid from IV bag or with use of volumetric pump. In our institution, we use buretrol/ volumetric pump in infants less than 10 kg and microdrip infusion in patients between 10–20 kg to prevent such complications. In sicker patients with cardiac, liver or kidney diseases, placing fluids on an infusion pump is essential to prevent volume overload. Frequent assessment to check for peripheral IV dislodgement and extravasation of fluids should be done to prevent distal limb ischemia and compartment syndrome.

Picture shows Buretrol which is a type of volumetric pump used in neonates and small children

The aim of fluid resuscitation is to restore effective arterial blood volume (intravascular volume), hemodynamic stability and organ perfusion. Repletion of fluids mostly depends on the severity and speed of fluid loss. Fasting fluid deficits are calculated by the number of hours for which fluids are restricted with the hourly maintenance fluid requirement. In 1975, Furman et al. proposed to replace 50% of fasting fluid deficit in first hour and 25% in the second and third hours. These guidelines were further simplified for trauma patients by Berry et al [35]. For patients who are fasting for 6–8 h preoperatively the author recommend giving 25 ml/kg in first hour for children 3 years and younger. In children 4 years and over they recommend decreasing the rate of fluids administered to 15 ml/kg. In subsequent hours they advise titrating the fluids based upon severity of surgical trauma. Blood loss is replaced 1:1 with blood or colloids or 3:1 with crystalloids.

With the newer recommendations that allow clear liquids until 2 h before surgery, there is less preoperative fluid deficit and thus they require lesser replenishment. Therefore, the amount of IVF administration should be reduced accordingly in children with shorter fasting periods or receiving preoperative maintenance IVF.

Isotonic crystalloid solutions (LR or NS) are recommended for volume resuscitation of pediatric patients [36]. Colloids can be used to rapidly restore intravascular volume especially during circulatory instability when crystalloid alone are ineffective and blood transfusion is not yet indicated [37, 38]. Rapid expansion of plasma volume, maintenance of intravascular oncotic pressure and decrease risk of pulmonary edema are some of the theoretical advantage associated with colloid use [39].

Repletion of third space losses with intravenous fluids is being questioned lately. Third space losses are defined as accumulation of fluid in the interstitial compartment outside the cells and blood vessels rendering it unavailable to the circulatory system. Capillary leak induced by surgical trauma, inflammatory mediators and destruction of glycocalyx, a key structure of vascular barrier, permits such fluid shift. This loss varies from 1 ml/kg/hr for minor surgery to 20 ml/kg/hr. for major abdominal surgery. It has been mentioned as high as 50 ml/kg/hr. during exploratory laparotomy for necrotizing enterocolitis in premature infants [40]. Isotonic fluids were recommended to replace "third space losses". Recent studies in adults have shown that replenishment of third space losses leads to volume overload and further endothelial glycocalyx destruction [41]. Liberal fluid therapy may have adverse outcomes. In a recently published study, Sanford et al. compared postoperative outcomes associated with high volume intraoperative fluid administration in pediatric patients undergoing colectomy. The authors found increased length of stay, time to first meal, and supplemental oxygen requirement in patients receiving high volume fluid [42].

In the United States it is not a routine practice to administer dextrose containing fluids in healthy children under anesthesia. Certain group of patients more prone to develop hypoglycemia such as neonates, Beckwith-Wiedemann, hypopituitarism, adrenal insufficiency, glycogen storage disease, hepatic adenomas or liver failure, pancreatic islet tumors (insulinoma). Perioperative dextrose administration, frequent glucose monitoring and accordingly adjustment of rate of infusion is recommended in these patients.

Red blood cell transfusion should be considered depending on transfusion trigger based on comorbidities and clinical condition of the patient. Recent evidence suggests that there is increased morbidity and mortality with liberal blood transfusion in children [43, 44]. Every effort should be considered to optimize hematocrit and nutritional status preoperatively and utilize blood conservation techniques to avoid transfusion. Of note, Calcium containing solution like Hartmann solution and Ringers lactate are contraindicated with blood or blood related products due to concerns of coagulation and clot formation (Table 17.8).

Individualized goal directed fluid therapy should be considered to determine the optimum amount of fluid necessary to maintain or improve flow related parameters such as stroke volume. Recent studies in adult patients managed with goal directed fluid therapy has demonstrated better postoperative outcome [47–50]. Dynamic

Table 17.8 Transfusion Threshold in Children

Blood Product	Clinical Condition	Transfusion Threshold
RBC	**Infant < 4 months of age**	**Hemoglobin (gm %)**
	Preterm/term born anemic	12
	Chronic oxygen dependency	11
	Severe pulmonary disease	12–14
	Cyanotic heart disease	12
	Late anemia stable patient	7
	Acute blood loss(hemodynamic instability)	12
RBC	**Infant > 4 months of age**	**Hemoglobin (gm %)**
	Stable infant	7
	Infant/child with perioperative bleeding	8
	Infant/child with cyanotic heart disease with increase oxygen demand	9
	Child with thalassemia major	9
	Child with sickle cell disease if previous CVA or acute chest syndrome	9–10
	Child with sickle cell disease for major surgery	9–11 (HbS < 20% for major thoracic or neurosurgery)

Modified from Reeve K et al. Transfusion guidelines in children: I. Anaesthesia & Intensive Care Medicine [45] and M ZG. Management of Perioperative Bleeding In Children. Step by step review [46]

monitoring modes like pulse pressure variation, perfusion index and plethysmography variability index should be considered during assessment of volume status and fluid responsiveness [22]. There is still a paucity in literature regarding use of various goal directed fluid therapy tools such as esophageal doppler and pulse contour analysis in pediatric populations.

Intraoperative Fluid Therapy in Neonates

Neonates, both preterm and term, poorly tolerate any errors in fluid and electrolyte management. There is physiological weight loss of about 5–15% in first few days of life but they regain body weight with adequate intake. Poorly feeding newborn or those undergoing surgery right after birth are at a high risk of hypoglycemia, hypernatremia, and dehydration. Neonates have a higher percentage of total body water and a higher circulatory blood volume. Their large body surface area and higher metabolic rate results in greater evaporative losses. Thus they have proportionally higher fluid requirements as they have more total body water, large body surface area and increased basal metabolic rate which results in higher fluid and electrolytes turn over. Prematurity increases neonatal fluid requirements. Neonatal kidneys have structural immaturity and high renovascular resistance, and thus have limited urine concentrating ability. Infant GFR and renal plasma flow are approximately half the

adult values with higher fractional excretion of sodium (2%) [51]. Hence both sodium conservation and regulation of extracellular fluid volume are impaired as compared to older children and adults and makes them vulnerable to fluid and electrolyte imbalance.

They also have myocardial immaturity due to relatively low contractile mass/gram of cardiac tissue. Thus they poorly tolerate hypo and hypervolemia. Neonates have limited ability to increase myocardial contractility and thus despite giving fluids there is inadequate increase in stroke volume, see Fig. 17.1. Modest fluid overload can result in cardiogenic pulmonary edema and prolonged ductal patency [52]. Fluid therapy in neonates is estimated and titrated based on current weight, clinical status, urine output and serum sodium concentration. Perioperative use of hypotonic or electrolyte free glucose containing fluid is still common practice in neonates (similar to Neonatal ICU) [38]. Administration of these hypotonic fluids in perioperative setting increases the risk of iatrogenic hyponatremia. They are also particularly sensitive to side effects of hyponatremia due to a variety of reasons as mentioned previously. A study done by Edjo Nkilly et al. [53] found direct correlation between the amount of intraoperative free water infusion and degree of hyponatremia postoperatively in neonates. The author recommended use of isotonic fluid in neonates during the perioperative period and close monitoring of plasma sodium level postoperatively.

Euglycemia is equally important in neonates. Newborns have limited glycogen stores and depend on gluconeogenesis. Blood glucose should be more than 45 mg/dl to avoid neurological damage making them high risk for development of starvation induced hypoglycemia. Thus, glucose infusion is commonly done intraoperatively in neonates. Dutta et al. [54] compared the effects of intraoperative infusion of 1% and 2% dextrose in Ringer lactate (@10 ml/kg/hr) in low birth weight neonates. They demonstrated effective glucose homeostasis in the studied IV fluids, but 1% dextrose containing fluid aids catabolism, insulin resistance, rebound hyperglycemia and acidosis. Thus, the author concluded 2–4% dextrose containing fluids more appropriate during neonatal surgery.

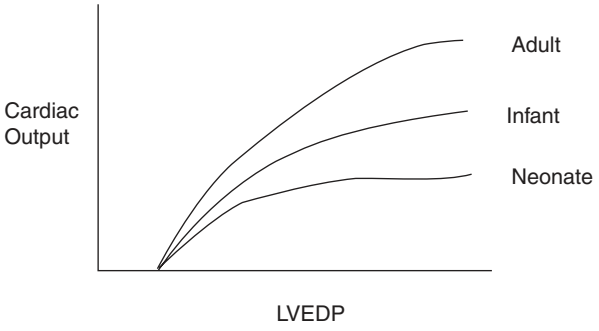

Fig. 17.1 Frank-Starling Curve

Postoperative Fluid Management and Hyponatremia

Early postoperative oral intake and enteral feeding should be encouraged. Children with non- functioning gut or ileus, respiratory insufficiency, neurological impairment or critical illness often require maintenance IVFs. Fluid therapy should meet routine maintenance requirements and replacement of ongoing water and electrolytes (urine, sweat, stool and nasogastric or ostomy output).

Under replacement of water losses can lead to volume depletion and hypernatremia while excess water replacement or more then excretory capacity can lead to volume overload and hyponatremia. Hypotonic fluid administration associated with higher incidence of postoperative hyponatremia in various randomized control trials and meta-analyses [16, 55].

Symptoms of hyponatremia vary from headache, nausea, poor balance to seizures and coma depending on sodium levels in plasma as shown in the Table 17.9.

Pediatric patients are more susceptible to side effects of hyponatremia than adults [15]. Pediatric brains have less room for expansion secondary to smaller skull size. Brain size reaches full growth by the age of 6 years but skull takes longer time to attain adult size (16 years), thus any brain swelling is poorly tolerated by children. Hence, there is increased incidence of brain injury and death reported with hyponatremia in the pediatric population. In a recently published guideline, American Academy of Pediatrics recommends that patients 28 days to 18 years of age requiring maintenance IVFs should receive isotonic solutions with appropriate potassium chloride and dextrose because they significantly decrease the risk of developing hyponatremia (evidence quality: A; recommendation strength: strong) [56]. Of note, this guideline does not apply to children with neurosurgical disorders, congenital or acquired cardiac disease, hepatic disease, cancer, renal dysfunction, diabetes insipidus, voluminous watery diarrhea, or severe burns; neonates who are younger than 28 days old or in the NICU; or adolescents older than 18 years old.

Clinical Situations Requiring Special Consideration

A. **Children receiving Total parenteral nutrition(TPN)**
Critically ill patients often present to the operating room with ongoing TPN infusion. Caution should advise while accessing dedicated TPN infusion

Table 17.9 Severity of Hyponatremia and corresponding Symptoms

Sodium level(mEq/L)	Clinical features
130–135	Asymptomatic or usually present with symptoms of underlying pathology
120–129	Weakness, lethargy, headache, nausea, muscle spasm
<120	Seizure, coma, respiratory arrest, death

[a]Clinical presentation usually varies depending on duration and severity of hyponatremia

intravenous lines due to risk of contamination and infection. TPN usually consists of two separate infusions: glucose/protein solution and intralipid solution. Intralipid infusion is usually discontinued during surgery due to concern of contamination as well drug drug interaction. It can act as lipid sink with lidocaine use for treatment of arrhythmia intraoperatively. Abrupt discontinuation of glucose/protein infusion without supplementation of glucose can lead to perioperative hypoglycemia. Frequent blood glucose monitoring intraoperatively and accordingly adjustment of TPN or dextrose infusion is recommended.

B. **Sickle Cell Disease**

Patients with sickle cell disease (SCD) unfortunately present to the operating room commonly for various procedures. The full perioperative care is beyond the scope of this chapter. However, the fluid management and exchange transfusion is important to review. SCD is characterized by a mutation which causes the hemoglobin molecule to change shape and polymerization under circumstances of dehydration, acidosis and hypoxia [57]. Patients with SCD are often admitted the day before surgery to ensure overnight hydration, or at the very least are encouraged to participate in a liberalized NPO strategy and to drink clear liquids up until 2 h prior to surgery. Dehydration may predispose to vasocclusive crisis, and consequently some recommend that maintenance fluids be given at 1.5 times the normal rate [58]. A commonly debated topic with SCD patients is the role of simple or exchange transfusions. Simple transfusion refers to administering blood with the goal of achieving a hemoglobin level of 10 g/dL. An exchange transfusion consists of removing a certain amount of the patient's blood while simultaneously giving back the same amount of blood. The end goal is to achieve a hemoglobin of 10 g/dL and a hemoglobin S level of 30% or less. This allows for increasing the oxygen carrying capacity of the blood and also decreasing the amount of hemoglobin S thereby preventing sickling and any vasocclusive crisis. Studies have shown that simple transfusions are equally as effective at reducing SCD related complications in patients as exchange transfusion, and simple transfusions are less likely to have a transfusion related morbidity than exchange transfusions [59].

C. **Pyloric Stenosis**

Pyloric Stenosis is a congenital thickening of the outlet of the stomach which causes an obstruction of the alimentary tract. Presentation is typically in the neonatal period, around 3 weeks of life. The obstruction results in persistent and the characteristic projectile vomiting. The metabolic consequence is initially a hypokalemic, hypochloremic alkalosis, with a compensatory respiratory acidosis manifested by hypoventilation. With progressive dehydration and development of shock the neonate may have a metabolic acidosis with hyperventilation and a respiratory alkalosis, however this is the less common presentation. The important thing to remember is that pyloric stenosis is a medical emergency, not a surgical emergency. It is imperative for the patient to undergo medical treatment in the form of fluid resuscitation prior to going to the operating room for pyloromyotomy. The medical fluid resuscitation consists of calculated volumes of D5 in normal saline or lactated ringers according to the degree of dehydration.

Once the fluid deficit has been replaced, maintenance fluids with D5 with ¼ saline with potassium chloride can be started [60, 61].

D. **Mitochondrial Disease**

Mitochondrial Disease was once thought to be a rare disease, although the incidence of this disease is estimated to be about 1 in 4–5000 births. Mitochondrial diseases are complex, heterogenous and display varying penetrance making it difficult to cleanly group them into categories and develop a simple treatment plan. Additionally despite the fact that mitochondria are inherited solely from the mother, siblings may present with heteroplasmy and thus the sibling of a child who underwent an anesthetic without complications may experience complications with the identical anesthetic. Mitochondrial disease impacts the high energy utilizing organs such as a brain, heart and muscles. These patients present with seizures, encephalopathies, cardiomyopathies, and myopathies. Despite the variation in these patients, one common approach is to avoid a metabolic burden, hence avoiding prolonged fasting, hypoglycemia, acidosis and hypovolemia is essential in keeping these patient safe during the perioperative period. Exactly which intravenous fluids to use is complicated. Generally it is best to avoid hypoglycemia as these patients are unable to rely upon stored substrates of energy. The one exception to this is those on ketogenic diets for seizure control; those patients should not have glucose in their fluids. Periods of hyperglycemia are not well tolerated as well, which makes it prudent for the anesthesiologist to closely monitor blood glucose levels. Lastly, some patients with mitochondrial disease are unable to metabolize lactate, thus it is imperative to avoid lactate containing fluids in these patients [62].

E. **Preload Dependent Conditions:**

Certain cardiac lesions depend upon adequate preload in order to maintain cardiac output. These lesions include aortic stenosis, hypertrophic cardiomyopathy, and hypoplastic left or right heart syndrome. The latter requires adequate venous return as pulmonary blood flow has no ventricle assisting it, and relies on passive blood flow. Patients with aortic stenosis and hypertrophic cardiomypopathy require adequate preload for maintenance of cardiac output in a ventricle with decreased compliance and also with an increased left ventricular end diastolic filling pressure. Additionally maintaining adequate preload will prevent obstruction of the outflow tract during mid to late systole which is important in subaortic stenosis and hypertrophic cardiomyopathy. In these patients emphasizing the importance of drinking clear liquids up until 1 or 2 h pre procedure will help keep these patients hydrated and preventing devastating consequences during induction when systemic vascular resistance and heart rate are often altered. In some cases, a preinduction IV is crucial and induction can be safely done with the administration of intravenous fluid [63, 64].

F. **Glycogen Storage Disease**

Glycogen Storage Diseases (GSD) encompass a series of disorders resulting from enzyme deficiencies of glycogen metabolism, both synthesis and degradation. It is a relatively uncommon disorders with a frequency of 1 in 20,000 live births. Patients present with hypoglycemia, glycogen accumulation and organ

failure. When these patients present for surgery special consideration must be made for fasting times, intravenous fluid choice and glucose monitoring. IV access can be difficult as these children have had frequent blood draws, and intravenous placements for a wide variety of procedures. GSD type I, von Gierke disease is a disorder of glucose-6-phosphatase or glucose-6-phosphatase transporter. The implications of this defect impairs the production of glucose via gluconeogenesis or glycogenolysis leading to hypoglycemia. Hence perioperative treatment must include appropriate NPO guidelines ideally keeping formula going until 6 h and cornstarch until 2 h preprocedure, dextrose containing fluids such as D10 0.45% NS along with frequent glucose monitoring perioperatively [65].

G. **Kidney transplants**

These patients are often dehydrated preoperatively due to preoperative dialysis and starvation. They also need optimal fluid resuscitation to improve graft function, with some studies recommending for a blood volume of 70 mL/kg [66]. Potassium-depleted fluids, such as 0.9% saline or Normosol were historically recommended in kidney transplant patients perioperatively for fear of hyperkalemia. A recent prospective randomized double blind trial done in adults undergoing kidney transplantation showed that ringer lactate was associated with less hyperkalemia and acidosis as compared with NS and is a safe choice for IV fluid therapy in patients undergoing kidney transplantation [67].

Conclusion

Perioperative fluid management in children requires a thorough understanding of preoperative condition, and expected fluid shifts, fluid loss and blood loss during the procedure. Maintenance of normal homeostasis and prevention of metabolic derangement are the cornerstone of perioperative fluid therapy. Neonates and small infants especially require precise fluid selection and delivery. In general, avoiding prolonged NPO times is discouraged, balanced isotonic electrolyte solutions are recommended in all age groups in order to avoid hyponatremia, and the addition of glucose should selected based upon specific patient characteristics.

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Restricted Versus Liberal Fluid Management Pros and Cons

18

David Liska

Abstract

Perioperative maintenance of adequate intravascular volume status is important to achieve optimal outcomes after surgery, but there are controversies regarding the appropriate volume of fluid therapy. Multiple small and some larger randomized controlled trials have demonstrated that liberal fluid management is associated with higher risk for poor postoperative outcomes, including postoperative ileus, increased length of stay, and overall morbidity. However, restrictive fluid regimens have not uniformly shown to be beneficial, with some studies showing increased risk for postoperative complications, especially acute kidney injury. To reconcile these conflicting findings, it is important to critically analyze the available data, while acknowledging differences in definitions, patient populations, and treatments. While some patients may benefit from goal directed fluid therapy, many patients can be optimally managed with a balanced fluid protocol aiming at maintenance of normovolemia.

Key Points

1. The volume of intravenous fluids administered during and after surgery has significant implications on patient recovery and outcomes.
2. Multiple randomized controlled trials have demonstrated that liberal fluid management with resultant volume overload and weight gain is associated with adverse outcomes, including higher rate of postoperative ileus, overall complications, increased hospital length of stay and costs.

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3. An overly restrictive fluid management protocol can also increase the risk for complications, in particular the risk for kidney injury, and especially if hypovolemia is not detected and corrected.
4. Optimal outcomes can be achieved with a fluid therapy protocol that focuses on maintenance of normovolemia by only replacing sustained fluid losses, while allowing for a fluid balance slightly above zero when needed.
5. Standardization of definitions and protocols is essential to optimize patient management and to facilitate further research.

Introduction

The goal of perioperative intravenous fluid (IVF) therapy is to reestablish and maintain normal physiology and organ function by using the appropriate volume of the correct fluid to achieve a state of homeostasis. Determining the correct volume of perioperative IVF has become an active area of research over the last few decades. The multitude of trials and reviews published on this topic, some with conflicting results and conclusions, highlight the controversies that have emerged over time. While there still remains a lack of standardized terminology in the literature, IVF regimens for abdominal surgery have been classified as restrictive (<1.75 liters per day), balanced (1.75–2.75 liters per day), and liberal (>2.75 liters per day) [1]. Liberal fluid management in most surgical patients was still the norm in the 1990s. However, with data showing that volume overload following surgery is common and detrimental to patients' safe recovery from surgery, restrictive fluid management was recommended and became an important component in many enhanced recovery after surgery (ERAS) pathways. On the other hand, more recently, studies have shown that overly restrictive fluid management strategies can also lead to morbidity, in particular with regards to postoperative kidney injury [2]. Goal-directed fluid therapy (GDFT), using various invasive or non-invasive measurements of volume status and/or end-organ perfusion, promises a bespoke approach to fluid therapy. However, indiscriminate use of GDFT devices may prove not to be practical or cost-effective and has not consistently demonstrated to be of benefit when compared to non-goal-directed judicious fluid management [3]. This chapter will review the current state of evidence regarding optimal perioperative fluid volume management strategies.

State of the Evidence

Traditional teachings in perioperative fluid management focused on the correction of hypovolemia caused by a confluence of assumed factors including: Preoperative fasting, mechanical bowel preparation, intraoperative acute blood loss, anesthesia-induced vasodilation, and surgery induced "third-spacing" of fluids [4]. This approach to fluid management was shown to result in the administration of approximately 6 L on the day of surgery and around 3 L daily on the first 3 postoperative

days, which was associated with a 3–4 kg postoperative weight gain [5, 6]. In the early 2000s this traditional approach to perioperative fluid management was challenged by several randomized controlled trials (RCTs). There exists significant heterogeneity between these trials, as some differ in their definition of what is considered liberal versus restrictive fluid management. Most trials reviewed here focus on major abdominal surgery, with a predominance of these focusing on colorectal resections, however some trials also included other abdominal surgeries. The majority of trials were relatively small, with many RCTs including less than 100 patients, with the distinct exception being the trial by Myles et al. [2], which included 3000 high risk patient undergoing abdominal surgery. It is also important to note that the period for fluid therapy and outcome endpoints were inconsistently defined with the primary outcome being different across these trials, albeit with significant overlap among secondary outcomes (Table 18.1).

Fluid Management and Postoperative Gastrointestinal Recovery

Postoperative Gastrointestinal (GI) dysfunction or postoperative ileus (POI) remains a major problem after abdominal surgery, increasing perioperative complications, postoperative hospital length of stay (LOS), and costs. Preclinical studies [7] demonstrated that GI edema increases gastric emptying time, suggesting that perioperative volume overload may be an important contributor to POI. Liberal fluid resuscitation can also lead to splanchnic edema which may result in increased abdominal pressure with decreased mesenteric blood flow, which in turn elicits tissue hypoxia and ultimately leads to ileus and anastomotic complications [8, 9]. To assess the effect of fluid management strategy on postoperative recovery of GI function, Lobo et al. [5], in an early small RCT (n = 20), demonstrated that liberal fluid management was associated with significantly longer gastric emptying times, delayed return of bowel function (flatus 4 vs 3 days; stool 6.5 vs 4 days) and significantly longer length of stay (LOS) (9 vs. 6 days, p = 0.001). There was also increased incidence of postoperative complications when compared to the restricted group. A RCT by Nisanevich [10], examining the effects of fluid management on postoperative morbidity and mortality, with return of bowel function as a secondary outcome, found that patients with liberal fluid management passed flatus and stool significantly later (flatus: 4 vs. 3 days; $P < 0.001$; stool: 6 vs. 4 days; $P < 0.001$). A just recently published large retrospective study of 4205 patients undergoing colorectal surgery within the context of a well-established ERAS pathway also confirmed the importance of fluid management on GI recovery [11]. In this patient population, POI occurred in 9% and on multivariate analysis was significantly associated with day of surgery fluids of >3 L (OR = 1.65 (95% CI, 1.13–2.41); P = 0.009) and postoperative day 2 weight gain of >2.5 kg (OR = 1.49 (95% CI, 1.01–2.21); P = 0.048). Not all studies demonstrated a difference in GI recovery based on fluid management. MacKay et al. [12] randomizing 80 patients undergoing colorectal surgery to restricted or liberal fluid regimens, did not find a difference in time to first flatus (2.9 vs. 2.9 days; P = 0.466) or bowel motion (4.7 vs. 4.9 days; P = 0.802). Similarly, a

Table 18.1 Summary of selection of randomized controlled trials assessing the impact of restrictive versus liberal fluid therapy on outcomes

First author year	N Res/Lib	Surgery	Primary Outcome	Favors Res or Lib	Bowel Function[a] Res/Lib (days)	Complications Res/Lib	LOS Res/Lib (days)
Lobo [5]	10/10	Colectomy	Gastric emptying	Res	4/6.5[b]	1/7[b]	6/9[b]
Brandstrup [6]	69/72	Colorectal resections	Complications	Res	NR	21/40[b]	NR
Nisanevich [10]	77/75	Abdominal surgery	Complications	Res	4/6[b]	13/23[b]	8/9[b]
Kabon [17]	124/129	Colectomy	SSI	ND	NR	NR	7.3/7.0
MacKay [12]	39/41	Colorectal resections	LOS	ND	4.7/4.9	ND	7.2/7.2
Holte [13]	16/16	Colectomy	Pulmonary function	Res	2/2	6/1	3/2.5
McArdle [22]	10/11	AAA repair	Major complications	Res	NR	1/14[b]	8/16[b]
Gonzalez-Fajardo [26]	20/20	Abdominal vascular	LOS	Res	4.6/5.3	NR	8/12[b]
Vermeulen [27]	30/32	Abdominal surgery	LOS	Lib	3.7/3.5	12/5[b]	12.3/8.3[b]
Abraham-Nordling [19]	79/82	Colorectal resections	LOS	ND	3/2 (first flatus)	31/47[b]	6.0/6.0
Gao [28]	93/86 (age > 65)	Abdominal surgery	Complications	Res	NR	31/39	NR
Peng [29]	84/90	Abdominal surgery	Complications	ND	NR	46/86	NR
Myles [2]	1490/1493	Abdominal surgery	Disability free survival	ND	NR	AKI: 8.6/5.0[b]	6.4/5.6

Res Restricted group, *Lib* Liberal group, *ND* No difference

[a]First passage of stool, *LOS* length of stay, *NR* not reported, *SSI* surgical site infection, *AKI* acute kidney injury

[b]$P \leq 0.05$

RCT by Holte et al. [13], including 32 colorectal surgery patients, found no difference in the return of bowel function or GI transit time, determined by radio-opaque marker transit study. On meta-analysis of 8 trials assessing POI [14], patients in the restricted group had a shorter time to first flatus in comparison with the liberal group (pooled difference in the mean = −0.67, 95% CI −1.28 to −0.06, P = 0.031). Given the significant impact of POI on postoperative recovery and LOS, avoiding fluid overload has become an integral component of most ERAS pathways.

Fluid Management and Surgical Site Infections

Surgical site infections (SSIs) remain a significant cause of patient morbidity and mortality, and are the third-most common source of hospital-acquired infection [15]. SSIs are relatively common, occurring in up to 20% of abdominal procedures, prolong the length of hospital stay and escalate hospital costs. Since many SSIs are considered preventable, they have become a key indicator of quality of care. SSI prevention is complex and requires the integration of a range of measures before, during, and after surgery [16]. Perioperative fluid therapy can play an important role in reducing risk of SSIs. With volume status being one of the important factors determining end-organ perfusion and tissue oxygenation, it is only logical that perioperative fluid management could have implications on wound healing and SSIs. Since SSIs are an important quality metric, studies have examined the effect of liberal versus restrictive fluid therapy on SSIs as primary or secondary outcome. In a relatively large RCT by Kabon et al. [17], where 253 patients undergoing open colorectal resections were randomized to restrictive versus liberal fluid administration, they authors hypothesized that a liberal fluid regimen would result in increased tissue oxygenation and thereby decrease surgical wound infections following colorectal surgery. However, no difference in surgical site infections or wound healing rate was found, suggesting that liberal fluid administration does not decrease the risk for SSIs. Most other RCTs comparing liberal to restricted fluid management were not specifically designed for SSI as outcome. The RCT by Brandstrup et al. [6], examining overall post-operative complications, found double the number of minor wound related complications (infection, hematoma, or dehiscence) in the liberal group (18/72 vs. 9/69) when compared to the restricted group. In the RCT by Nisanevich [10], wound complications were also more common in the liberal group (11/75 vs. 7/77). In a systematic review and meta-analysis published in 2016 [18], wound infections were found to be more common in the liberal group. On the other hand, the RCT by Nordling et al. [19], comparing an "extremely" restricted fluid protocol to a standard regimen, found no difference in wound infections between the two groups (10/79 vs. 11/82). Holte et al. [13] found an increase in SSIs and wound complications with restricted fluid management (5/16 vs. 0/16), including 3 anastomotic leaks in the restricted group. Similarly, the large 2018 trial by Myles [2], found that SSIs were more common in the restrictive group (245/1481 vs. 202/1487; p = 0.02), although this was not statistically significant when adjusting for multiple comparisons. In the absence of more trials powered to specifically

assess the impact of restricted versus liberal fluid management on wound infection, it remains controversial if current perioperative fluid management strategies directly impact the risk for developing SSIs.

Acute Kidney Injury

With avoidance of hypervolemia becoming a recommended component of ERAS pathways, there was an increase in reports of the potential harm in restrictive fluid regimens. In particular, there was concern for acute kidney injury (AKI), due to renal hypoperfusion in an overly restrictive protocol or due to renal interstitial edema in settings of hypervolemia [20, 21]. Brandstrup et al. [6] reported a significantly lower serum creatinine in the liberal group upon arrival in the recovery room, however there was no difference found in the subsequent days. McArdle et al. [22] measured the urinary albumin/creatinine ratio in 22 patients undergoing abdominal aortic aneurysm repair randomized to restricted or liberal fluid administration. They reported a significantly higher value in the liberal group, suggesting impaired renal endothelial function due to volume overload. However, there were no cases (0/11) of renal failure reported in the liberal group compared with one case (1/11) in the restricted group. The most significant study to highlight the potential detrimental consequence of restricted fluid protocols on renal function was the international multicentered RELIEF trial by Myles et al. [2] that randomized 3000 high risk (age $\geq$ 70, or heart disease, diabetes, renal impairments, or morbid obesity) patients to liberal or restrictive IVF regimen. The primary outcome was disability-free survival at 1 year. The investigators found that a restrictive fluid regimen was not associated with a higher rate of disability-free survival than a liberal fluid regimen but was associated with a higher rate of acute kidney injury (8.6% vs 5.0%; $P < 0.001$) and there was a trend towards higher requirement of renal-replacement therapy (RRT) in the restricted group (0.9% vs. 0.3%; $P = 0.048$). Despite the large sample size in this trial, there are some limitations that temper the conclusions one can draw from this trial. The study's pragmatic design lead to perioperative care that was not standardized and there was a wide variation in the anesthetic and analgesic techniques, including use of epidural analgesia, variable intraoperative hemodynamic management, and variable postoperative care. The total fluid volume administered during and up to 24 hours after surgery was 3.7 versus 6.1 L in the restrictive and liberal groups, respectively. These amounts are similar to typical restrictive and liberal fluid strategy totals. However, the reported increase in body weight was relatively minor—1.6 kg in the liberal fluid group and only 0.3 kg in the restrictive fluid group, which represent increases that are far lower than those in other fluid management trials. This modest increase in body weight, together with the absence of a protocol driven monitoring and standardized response to postoperative hypovolemia, oliguria, and hypotension may have contributed to the increase in AKI events in the restrictive group. The authors are therefore correct in interpreting their results cautiously and they conclude that a modestly liberal fluid regimen is safer than a truly restrictive regimen.

Overall Complications and LOS

In one of the seminal trials examining perioperative fluid management, Brandstrup et al. [6], examining post-operative complications as primary outcome, randomized 172 patients undergoing colorectal surgery to either liberal or restricted fluid management. The restricted fluid management protocol was associated with a significant reduction in overall complications (33% vs. 51%, P = 0.003). This was true for both major (such as anastomotic leak, sepsis, bleeding, and pulmonary edema requiring assisted ventilation) and minor (superficial wound infections, pneumonia, and urinary tract infection) complications. Independent of fluid management protocol being followed, there was a dose-response relationship between complications and increasing volumes of fluid and increasing body weight, confirming the importance of volume overload on postoperative outcomes. Since then there have been several systematic reviews and meta-analyses published to integrate the data generated from many different RCTs, especially with regards to overall perioperative outcomes and hospital LOS. Considering the conflicting results from individual RCTs, it is not surprising that meta-analyses are unable to provide conclusive evidence when combining data from these heterogenous patient populations. However, of note, on a meta-analysis by Jia et al. [14] (published in 2017), despite there not being a statistically significant benefit to restrictive fluid therapy with regards to overall complications (OR = 0.59, 95% CI 0.34–1.04, P = 0.068), hospital LOS was significantly shorter with a restrictive regimen (pooled difference in the mean = −1.51, 95% CI −2.90 to −0.12, P = 0.033).

An important meta-analysis performed by Varadhan and Lobo [1] helped reconcile some of the conflicting RCT results by standardizing the definition of fluid management strategy based on actual daily volume received (as detailed in our introduction above) and then reclassified study populations from RCTs into three groups: underhydration, normovolemia or balanced, and fluid overload. Without reclassification into these internally more consistent categories, meta-analysis showed no difference overall complications and LOS between liberal and restricted fluid therapy. However, following reclassification, meta-analysis showed that patients treated with a fluid balance (normovolemia) versus fluid imbalance had significantly fewer overall complications (RR 0.59; 95% CI 0.44–0.81) and shorter LOS (weighted mean difference—3.44 days (95% CI −6.33 – −0.54). A more recently performed meta-analysis on fluid restriction following abdominal surgery by Shen et al. [23] demonstrated similar findings. They included 16 RCTs with a total of 2341 patients that were treated with a restricted regimen and 2337 patients receiving liberal regimen (2983 of these patients are from the study by Myles et al. [2] discussed above). All sixteen studies compared the total complication rates between restricted and standard regimens in patients undergoing abdominal surgery. Similar to prior meta-analyses [1, 14], there was no benefit of a restricted regimen in reducing overall postoperative complication when combining the conflicting data from all included RCTs. However, on subgroup analysis, when assessing studies where the postoperative mean patient weight gain difference between liberal and restricted groups was ≥2 kg (8 RCTs with a total of 662 patients), there was a

significantly reduced risk for postoperative complications in patient on restricted protocols (RR 0.67, 95% CI 0.57–0.79). These results again confirm that the benefits of restricted fluid management are most apparent when compared to liberal fluid management that resulted in substantial hypervolemia associated with postoperative weight gain.

Normovolemia or Balanced Fluid Administration

Taken together, the above studies clearly show that excessive perioperative administration of intravenous fluid, which was common in traditional liberal approaches to fluid therapy, should be avoided. However, when following overly restrictive regimens, one risks complications related to hypovolemia, without any significant benefits compared to a moderately liberal protocol. The concept of an optimal "Goldilocks zone" of fluid management which lies between traditional liberal protocols and the strict fixed-volume, zero-balance approaches, has also been confirmed by recent large retrospective studies. Thacker et al. [24] studied large data from the Premier Research Database including patients undergoing colon (n = 84,722) or rectal surgery (n = 22,178) and hip or knee replacement (n = 548,526) to analyze the variability in perioperative (day of surgery) fluid utilization and its relationship with outcomes. A wide range of fluid utilization was observed, with 25% of patients receiving less than 1.7 L for colon, 1.5 L for rectal, and 1.3 L for hip/knee surgeries. On the other hand, 25% of patients received more than 5.0 L for colon, 5.4 L for rectal, and 4.1 L for hip/knee surgeries. When classifying patients into 3 groups based on fluid utilization they found that in colorectal and orthopedic surgery both low and high fluid volumes were associated with worse outcomes including increased LOS, POI, and hospital costs. This U-shaped association between the volume of fluid administered and postoperative complications was also demonstrated in a large retrospective registry study by Shin et al. [25] Here, 92,094 patients undergoing noncardiac surgery were evaluated with the primary exposure variable being intraoperative fluid administered and outcomes being 30-day survival, respiratory complications, AKI, LOS, and costs. Liberal fluid volumes in the highest quintile of fluid administration were significantly associated with respiratory complications whereas both liberal and overly restrictive (lowest quintile) volumes were significantly associated with acute kidney injury. Moderately restrictive volumes were consistently associated with optimal postoperative outcomes, including decreased mortality, LOS, and costs.

Summary and Considerations for Current Practice

While further well-designed prospective trials regarding some of the nuances of intraoperative fluid therapy are still needed, the current data demonstrates that both liberal and overly restrictive fluid regimen can significantly complicate a patient's recovery following surgery. This confirms the important role appropriate

perioperative fluid management, with the avoidance of excessive weight gain and hypovolemia, has in the surgical patient's safe and swift recovery from surgery. While some patients may benefit from cardiac-output driven GDFT, the majority of patients can safely be managed with a protocol that focuses on maintenance of normovolemia, which can usually be achieved by only replacing sustained fluid losses while allowing for a fluid balance slightly above zero when needed. Postoperatively, patients managed in the context of an ERAS protocol will usually not need any supplemental IVF. However, patients need to be monitored for signs of hypovolemia and end-organ hypoperfusion which then needs to be treated with supplemental IVF to avoid complications. The wide variability of fluid protocols currently employed, highlight the importance of developing institutional patient-specific protocols that should be rigorously implemented.

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Artificial Intelligence for Perioperative Fluid Management

19

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Abstract

Artificial Intelligence is an evolving area of computational science with increasing research and real-world applications in healthcare. In the perioperative patient population, increased use of AI is being found to improve quality of care and prevention of adverse events. One such area relates to prevention of hypotension and management of systemic blood pressure. Novel machine learning models to estimate fluid status and predict hypotension have been proposed. We discuss the current state of research and application of these machine learning models for perioperative fluid management.

Key Points

1. Research and development in application of artificial intelligence is expanding in perioperative fluid management.
2. Machine learning techniques including feature engineering for image interpretation and neural networks are being applied to assess hemodynamic status of patients.

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3. Clinical decision support for personalized decision making and advanced explainable analytics will provide pre-emptive and precision guidance for therapy.
4. Cohort analysis on large populations can be performed for quantitative and qualitative performance review using various learning techniques.

Introduction to Artificial Intelligence

Artificial Intelligence (AI) is a computational science which attempts to replicate human cognitive function. It has many fields of study, which include machine learning (ML) and deep learning, both of which are now commonly being researched and implemented in healthcare. Over the last decade, research in this field, especially related to critically ill patients, has expanded significantly [1]. ML is a subset of AI, which uses computational power to derive complex statistical modeling and thereby create continuously improving solutions. Deep learning uses layers of computation to generate solutions, which have a complex architecture and relationship. Neural networks are part of ML, which replicates the neural transfer of information across a synapse, as in the human brain. Learning in these networks occurs both through forward transmission of input data to output (forward propagation) and uniquely backward transmission (back propagation) (Fig. 19.1).

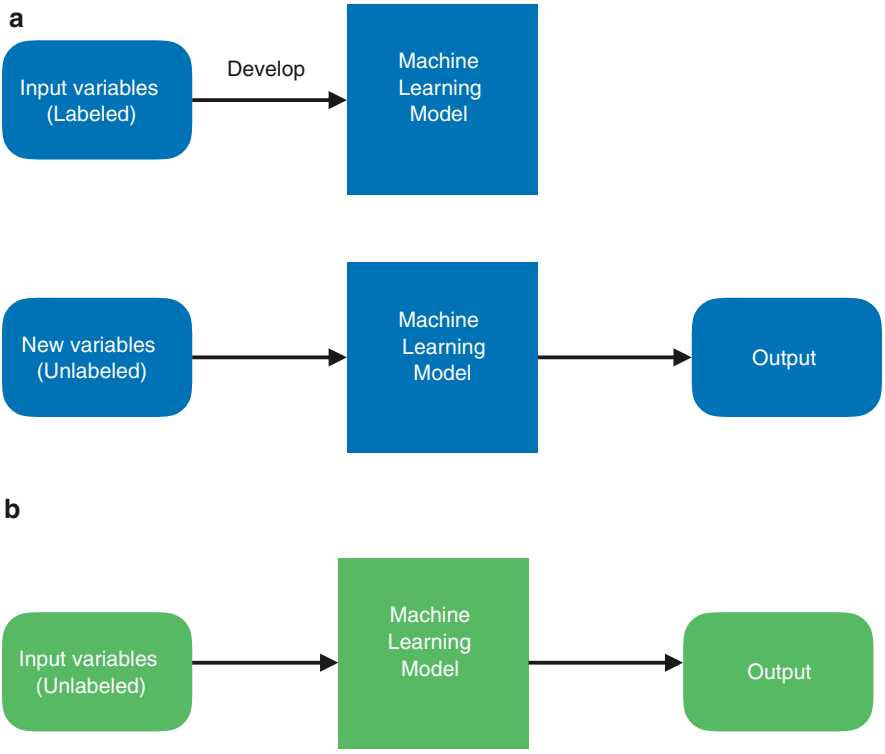

Fig. 19.1 Output generation from input data using (**a**) Supervised machine learning model and (**b**) Unsupervised machine learning model

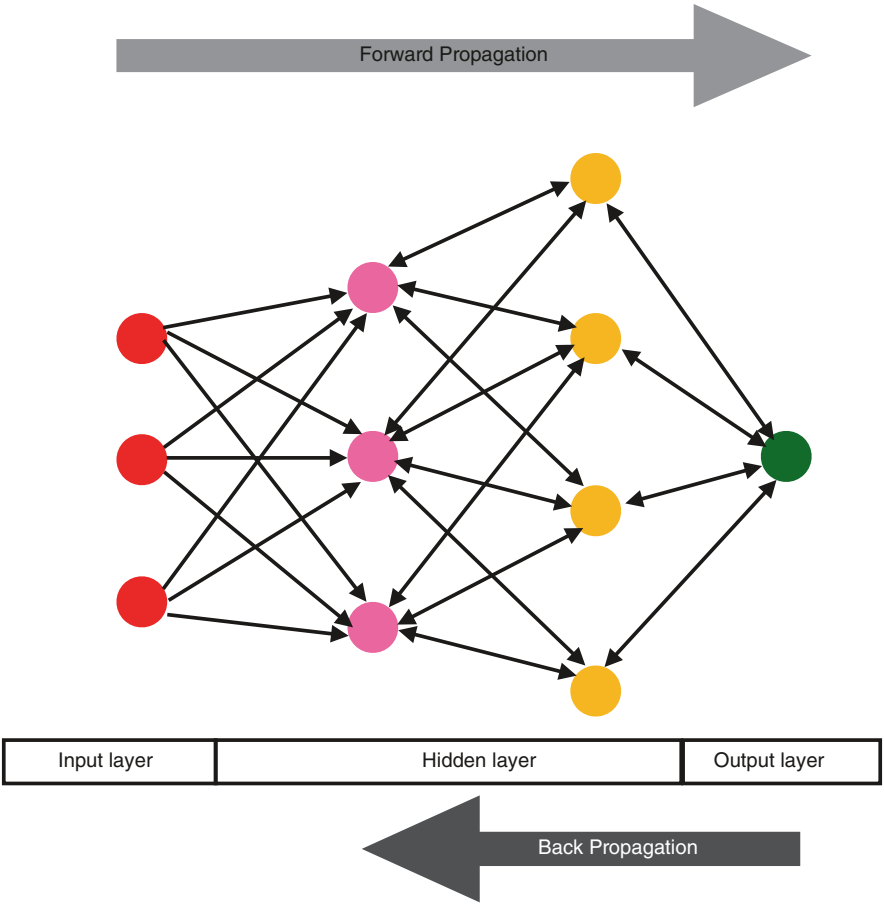

Fig. 19.2 Artificial neural network showing, (**a**) Input data layer, (**b**) Hidden processing layers, (**c**) Output layer. Forward propagation and back propagation of the data resembles the neural architecture of data propagation in human neural network

Broadly, three different classes of ML exist, including supervised learning, unsupervised learning and reinforcement learning (Fig. 19.2). In supervised learning, labeled data is provided to "train" the model, which will be able to recognize and predict results from newly provided unlabeled data. Unsupervised learning does not require any provision of labeled data but makes associations between various data to make the best assumptions of the characteristics, patterns, and relationship within the provided data. Reinforcement learning is a newer and evolving field, especially in healthcare, where the model learns from an action in a given environment to maximize reward. Natural language processing (NLP) is another field of machine learning, where computational algorithms can interpret free text with high statistical accuracy.

Machine learning and deep learning themselves have various computational methods that harness the power of expanding electronic healthcare data to provide solutions, which are implementable in real or near time. In the perioperative areas,

their use has been seen in the development of prediction models, clinical decision support and analysis of clinical notes using natural NLP [2]. Most commonly, prediction models have been developed to predict early deterioration of clinical conditions and/or clinical outcomes [3, 4]. These models have not only been developed using patient vitals or laboratory data but rather use of multimodal data inputs including clinician notes, medications and test results, which have shown to generate better and more accurate models [5]. While AI in healthcare is mostly in research and validation phase, some early solutions have been developed and approved by US FDA (Food and Drug Administration) for clinical application, i.e. cardiovascular assessment (US FDA approve EchoMD AutoEF software for calculating left ventricular ejection fraction (https://cardiovascularnews.com/fda-approve-echomd-autoef-software-for-calculating-lvef/).

Fluid Status Measurements Using AI

Traditional methods of intravascular fluid status assessment in perioperative period have focused on combination of various discreet parameters such as: blood pressure, heart rate, urine output, central venous pressure, lactic acid level as well as advanced monitoring techniques: pulse pressure variability, ultrasonography of inferior vena cava, echocardiographic assessment of the heart, pulmonary artery catheter parameters and noninvasive cardiac output monitor variables amongst others.

Many of the variables derived from advanced monitors have been used in various combinations to assess patient's fluid status in the clinical practice, however, with an increasing number of data inputs accurate clinical interpretation may be challenging. The gold standard of estimation of left ventricular end-diastolic volume (LVEDV) is used infrequently and assessments of fluid responsiveness are more commonly applied.

Machine learning techniques offer the ability to not only analyze the relationship amongst individual variables but also complex waveform data in real time. The increasing number of studies are focused on the early prediction of patient deterioration using composite scoring systems composed of the traditional discrete measurements of vital signs. But now thanks to ML these variables can be monitored in real time and models provide an explanation of the predictions.

Featurization is a common technique in ML, where various data measurements are converted to numerical values and used to create complex derivatives for a better understanding of relationships amongst individual variables and generate an optimized output. This has been commonly applied in image interpretation such as computed tomography (CT) scans and waveform interpretation, such as arterial waveform analysis. Utilization of this technique in relationship with other data points is very useful in developing an interpretable neural network or other ML models. These models are being tested for application in the perioperative areas including the operating rooms and intensive care units.

Additionally, using ML's image recognition capabilities echocardiographic measurements can be automatically generated without the need for human

interpretation. High level of accuracy in automated estimation of cardiac functions including ejection fraction as compared to cardiologist interpretation has been recently demonstrated [6]. Assessment of outcomes in different patient populations using ML methods for fluid balance has also been demonstrated to be very useful [7].

The ideal model for intraoperative fluid administration guidance should have the following characteristic: patient-specific, highly predictive and well validated.

Applications of Predictive Analytics and Arterial Waveform Analysis

Hypotension has been consistently associated with complications in the patients undergoing surgical procedures as well as treated in intensive care units [8, 9] Unfortunately these findings come from retrospective studies, where the causal relationship cannot be established [8, 9]. Despite the fact that there is a good physiologic explanation of why hypotension can be responsible for the end-organ injury (in particular myocardial and kidney injury), prospective randomized trials showing causal relationship are scares [10]. Most clinicians agree that perioperative hypotension should be avoided and can be harmful, however, there is still debate what constitutes potentially harmful hypotensive event: absolute threshold below which blood pressure falls or combination of different thresholds crossed and cumulative time spent under given blood pressure thresholds [11]. The challenge facing clinician is the lack of well-defined definition of potentially consequential (harmful) hypotension and guidelines regarding the timing and form of best intervention. This has significant implications: hypotension is treated after it occurs and chosen treatment may not be the best choice for underlying pathophysiologic disturbance. Conceivably, a better alternative would be the prevention of hypotension all together by means specifically addressing underlying physiologic changes which lead to it.

In the era of sophisticated cardiovascular monitoring and ability to process a large amount of data in real time the possibility of being able to predict an impending episode of hypotension is becoming more realistic than ever [4, 12]. Algorithms derived from arterial waveforms (including waveform time, amplitude, area, segment slopes, complexity features, etc.) can predict hypotension, defined by MAP < 65 mmHg for at least 1 min [4, 12]. The Hypotension Prediction Index (HPI) software is already commercially available and has been clinically tested for its ability to predict the episodes of hypotension. Interestingly the sensitivity and specificity of HPI for predicting hypotension 5 min beforehand are 92% and 92%; it is 89% and 90% 10 min beforehand and 88% and 87% 15 min beforehand [6].

There is an ongoing investigation to assess if adding HPI software guidance to the information provided by the invasive arterial pressure monitoring during moderate-to high-risk noncardiac surgery reduces time-weighted average (TWA) intraoperative hypotension below a threshold of 65 mmHg [4]. Not only the software can predict the probability of future hypotension but also provide a recommendation of treatment based on the in-depth arterial waveform analysis [4]. In general, hypotension can be induced by any three factors alone or a combination of them:

hypovolemia, vasoplegia, or decreased myocardial contractility. Based on HPI algorithm clinicians can be presented with six potential interventions: fluids administration only, fluids and inotropes administration, fluids and vasopressor(s) administration, vasopressor(s) administration only, inotropes administration only, and observation. All recommendations are supported by established parameters describing the status and function of the circulatory system [4].

The concept of prevention rather than treatment of the hypotension seems to be very attractive in particular if one can tailor the intervention to correct the underlying cause of the foreseen decrease in blood pressure.

Quality and Performance Analysis of Fluid Management Using Machine Learning

Machine learning (ML) can help develop pathways for best perioperative fluid management. Unsupervised analysis of large surgical or intensive care unit patient's cohort is a simple way to identify subsets of patients sharing similarities, which may not be apparent to the clinicians. The power of ML is related to its ability to sift through a massive amount of data and detect patterns and similarities not comprehensible for the human brain due to its sheer volume. Additionally ML improves its predictive models as more data becomes available and can run the models in real time making prediction or treatment suggestion clinically relevant and actionable. Comparison of subsets based on outcomes further identifies the similarities and differences in patient, procedure characteristic and provided treatment. This initial insight into the clinical factors and treatment events differentiating groups with less favorable and more favorable outcomes allows generating hypothesis for further testing.

Maheshwari et al. using Clinical Variation Management (CVM) platform (Ayasdi, Menlo Park, CA) identified practice patterns in colorectal surgery in the Cleveland Clinic hospital network [7]. Software identified "best performing" group of patients based on desirable clinical outcomes such as short hospital stay, low readmission rate and overall low cost per case. The volume of intraoperative fluid administration was identified as one of the differentiating features between best and worst performing groups. These findings can be easily implemented into the near real-time compliance reporting system, which provides live decision support to the provider regarding optimal fluid administration strategy based on patient and procedure characteristic [7]. Keeping in mind that the individual provider accounts for the majority of variability in intraoperative fluid administration and fluid management may be affecting clinical outcomes, ML opens new possibilities to assure guidance and compliance with established fluid administration strategies [13, 14].

Appropriate fluid management is crucial in achieving optimal outcomes in critically ill patients as well. Unfortunately in clinical practice decisions about administration or withholding of fluid resuscitation are based on individual clinician judgment, which very often is inconsistent and introduces significant unjustified

variability into clinical practice. ML can be very helpful in predicting response to volume administration: a study by Zhang et al. used machine learning XGBoost model to develop a prediction model that can differentiate between volume-responsive (VR) and volume-unresponsive (VU) acute kidney injury (AKI) in intensive unit patients [15]. Using US-based critical care database (Medical Information Mart for Intensive Care (MIMIC-III)) authors developed model which was able to differentiate between patients who would and would not respond to fluid administration with an increase in urine output [15]. The model was developed on training set and validated on testing set (1:3 ratio), all routinely collected clinical and laboratory variables obtained within the first 6 h of ICU admission were evaluated for their ability to predict volume responsiveness. Urinary creatinine, blood urea nitrogen (BUN), age, and albumin were the important predictors of VR [15]. The potential benefit of model implementation cannot be underestimated; early fluid administration to VR patients can prevent progression of AKI while avoidance of fluid challenge can prevent consequences of volume overload in VU patients. Following the model prediction can improve appropriate administration of fluids early during intensive care unit stay to avoid both hypervolemia and hypovolemia [15]. All calculation related to the generation of volume responsiveness prediction can be done automatically and updated as new data points become available, making the model dynamic and responsive to real-time changes in patient condition, hence clinically valuable.

Sepsis-fluid Management Using AI for Critically Ill

Fluid management in sepsis is still a matter of the great debate [16], it seems however that inappropriate treatment with fluids and/or vasopressors can lead to suboptimal outcomes [17, 18]. Artificial Intelligence and ML can be used to develop a decision model on historical data to assist a physician in choosing optimal fluid treatment strategy. Komorowski et al. developed the AI Clinician, a computational model using reinforcement learning, which was able to dynamically suggest optimal treatments (intravenous fluids and vasopressors) for adult patients with sepsis in the intensive care unit (ICU) [19]. AI Clinician was built and validated on two large non-overlapping ICU databases containing data routinely collected: the Medical Information Mart for Intensive Care version III (MIMIC-III) was used for model development and the eICU Research Institute Database (eRI) for model testing [19]. Authors demonstrated that septic patients who received treatment doses of intravenous fluids and vasopressors similar to the doses recommended by the AI Clinician had the lowest mortality. When the clinicians' actual treatments varied from the AI Clinician's suggested treatment, this was the most common administration of too little vasopressor [19]. Described system and methodology could potentially be used in real-time, with patient data streaming from different electronic sources and fed predictive algorithm, which would suggest the most appropriate course of treatment. The ultimate treatment strategy will be made by physicians based on multiple sources of clinical data and subjective clinical judgment, however,

computational models can provide additional insight about optimal decisions, avoiding targeting short-term resuscitation goals instead of following trajectories toward longer-term survival [19].

Clearly, all research done so far has significant limitations, a major one being a lack of prospective clinical trials confirming the validity of predictive models. Also to the best of our knowledge no system has been successfully implemented in real clinical practice to show measurable benefits. Keeping in mind these limitations, future will show if the use of computer decision support systems is beneficial to better guide treatment strategies.

Future Directions

In the future, there is likely to be increasing number of validated applications which will be developed for clinician-guided perioperative fluid management (Fig. 19.3). These ML solutions are likely to be multimodal and will use data derived not just from the patient's vitals but also from other sources such as electronic health records and smart infusion pumps. Complex feature engineering is likely to play an important role in discovering the importance of each variable and assigning appropriate weight to improve accuracy and predictions. Advanced models using newer ML methods such as reinforcement learning will likely replace traditional methods such as supervised learning. We are likely to see image analysis, NLP and many other advanced ML techniques being used in the same solution.

For successful development and implementation of any of these solutions, clinical validation, explainable solution, workflow integration in a cost-effective manner will be the key. These AI solutions will likely integrate into our current monitoring

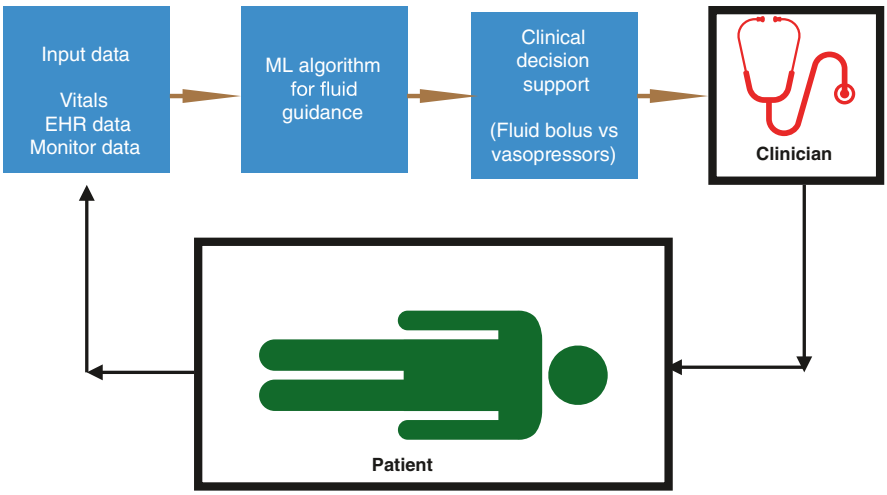

Fig. 19.3 Flowchart showing application of machine learning for perioperative fluid management

devices and provide interpretable and actionable results to clinicians through electronic health records or other mobile device applications. It will also be important that these AI solutions are not just delivering one or two "scores" or derived outputs but present a holistic picture of the patient condition with supportive clinical guidance as an end to end solution.

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Part II

Case Scenarios Management During Colorectal, Orthopedic, and Spine Cases

Case Scenario for Perioperative Fluid Management in Major Orthopedic Surgery

20

Wael Ali Sakr Esa

Abstract

Fluid management is a crucial issue for patients undergoing major orthopedic surgery, in which large blood loss, transfusions, fluid shifts, and high incidence of postoperative complications are important concerns. Fluid balance is a major contributing factor to postoperative morbidity and mortality. Persistent hypovolemia is associated with organ hypoperfusion, systemic inflammatory response syndrome, sepsis, and multiple organ failure. Fluid overload, on the other hand, is associated with edema, ileus, postoperative nausea and vomiting, pulmonary complications, and increased cardiac demands.

Key Points

1. Persistent hypovolemia is associated with organ hypoperfusion, systemic inflammatory response Syndrome, sepsis, and multiple organ failure.
2. Fluid overload is associated with edema, ileus, postoperative nausea and vomiting, pulmonary complications, and increased cardiac demands.
3. The goal of perioperative fluid management in major othropedic surgeries is to maintain intravascular volume, safeguard adequate perfusion of vital organs, and maintain acid-base balance and electrolyte balance.
4. There is still controversy between colloids versus crystalloids in fluid management.

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5. Trans-oesophageal echocardiography helps to better guide fluid management in critically sick patients undergoing major orthopedic surgeries with the potential of massive blood loss.

Introduction

Fluid management is a crucial issue for patients undergoing major orthopedic surgery, in which large blood loss, transfusions, fluid shifts, and high incidences of postoperative complications are important concerns. Fluid balance is a major contributing factor to postoperative morbidity and mortality. Persistent hypovolemia is associated with organ hypoperfusion, systemic inflammatory response syndrome (SIRS), sepsis, and multiple organ failure. Fluid overload, on the other hand, is associated with edema, ileus, postoperative nausea and vomiting, pulmonary complications, and increased cardiac demands [1].

Traditional methods to monitor the preload are based on measurements of pressure or volume, such as the mean arterial pressure (MAP), the heart rate, or the central venous pressure (CVP). However, these are static parameters and do not accurately reflect fluid responsiveness [2].

The optimal choice of resuscitation fluid has been the subject of intense debate for decades, with lack of definitive conclusion. Several recent publications cautioned that hydroxyethyl starches might be associated with an increased risk of acute kidney injury and renal replacement therapy, especially in septic or critically ill patients [3–6]. In June 2013, the US Food and Drug administration (FDA) released a warning concerning the use of hydroxyethyl starches in patients with sepsis, impaired renal function, or coagulopathies [7].

Albumin, like hydroxyethyl starch, has been associated with impaired coagulation and increased blood product transfusion rates after cardiac surgery [8]. However, albumin is still the preferred colloid to be used in critically ill patients.

Studies investigating the effect of infused fluid type on outcomes seem to be especially burdened by the limitations related to confounding factors.

The goal of perioperative fluid management is to maintain intravascular volume, safeguard adequate perfusion of vital organs (brain, heart, kidney, and gut), and maintain acid–base balance and electrolytes balance [9].

Case History

A 72-year-old male, American Society of Anesthesiologists (ASA) status 4, is scheduled for open resection of a pelvic tumor attached to the pelvic bones on both sides and surrounding the right iliac artery. The past medical history is significant for:

1. Ischemic heart disease—stress test negative for ischemia, ejection fraction = 40 ± 5%

2. Hypertension—on atenolol
3. Hyperlipidemia—on Crestor
4. Chronic obstructive pulmonary disease—on albuterol—stable
5. Diabetes mellitus—on metformin, HbA1C 7.4

Preoperative vitals: blood pressure (BP), 130/65 mmHg; pulse, 56/m; height, 181 cm (5′ 11″); weight, 90 kg (198 lb); body mass index (BMI), 27.5 kg/m^2; SpO_2, 96%.

Preoperative Management

The patient received an education session at the preoperative anesthesia clinic on the expected course of the perioperative period, especially regarding pain management, mechanical ventilation, potential massive blood and fluid transfusion, intensive care stay, and duration of hospitalization.

The pain control including epidural was discussed with the patient, but given the potential for massive blood loss we agreed on placing the epidural postoperatively after the patient becomes hemodynamically stable in the intensive care unit (ICU), off pressors, and acceptable coagulation profile and platelets were achieved.

The patient was allowed to drink clear liquids up to 2 h before surgery. He was also given a complex carbohydrate fluid to be used overnight and advised to stop drinking this fluid up to 2 h before surgery. The goal is to minimize the period of fasting and dehydration. In the preoperative area, a 16-gauge peripheral intravenous (IV) line was started, and a balanced crystalloid fluid-lactated Ringer's was started at 1 ml/kg/h.

Intraoperative Management

The patient was taken to the operating room where all the team members introduced themselves and their roles to the patient. According to the safe surgery checklist, a preoperative huddle was performed with the presence of the surgeon, anesthesiologist, and nurses. Four units of packed red blood cells (PRBCs) were ready before the start of the surgery.

Monitoring

The patient was monitored according to standards set by American Society of Anesthesiologists (electrocardiogram [ECG], noninvasive blood pressure, oxygen saturation, temperature). Anesthesia was induced with propofol (1.5 mg/kg), rocuronium (0.5 mg/kg), and fentanyl (1 mcg/kg). An arterial line was placed for perioperative hemodynamic management. Another two peripheral intravenous lines (14-gauge) were placed for fluid management.

An 8 French central venous catheter was placed in the right internal jugular vein under ultrasound guidance. A rapid infuser was available in the room—ready for use if needed—due to the proximity of the tumor to the right iliac artery and the size of the tumor.

A transesophageal echocardiography (TEE) probe was placed to monitor the volume status, emboli, and any regional wall motion abnormalities after suctioning the stomach with an orogastric tube. Suctioning the stomach will allow better transgastric imaging of the heart during the surgery.

Maintenance

Anesthesia was subsequently maintained with isoflurane (up to 1 MAC), using 50% oxygen and 50% air. Ketamine infusion at 5 mcg/kg/min and lidocaine infusion at 1 mg/kg/h were started for pain control. Intermittent boluses of fentanyl and hydromorphone were administered according to the patient's requirements.

Additional muscle relaxant was given as necessary to maintain one to two mechanical twitches in response to supramaximal stimulation (train-of-four stimulation) of the ulnar nerve at the wrist. Ventilation was mechanically controlled to maintain end-tidal carbon dioxide tension around 35 mmHg. Tidal volume used was set at 5–7 ml/kg lean body weight to keep the peak inspiratory pressure below 30 mmHg and a positive end-expiratory pressure of 5 mmHg. Temperature was monitored, and normothermia (core temperature ~ 36 °C) was the goal, and the temperature was maintained with forced-air warming and warming the intravenous fluids and blood used.

Fluid and Hemodynamic Management

Lactated Ringer's was used for maintenance, and normal saline was used in the tubings where blood was administered during the case. We used albumin to replace the blood loss and as boluses to enhance the stroke volume (SV).

Intraoperatively, the TEE was used to adjust the volume of the fluid infused. The transgastric midpapillary short-axis view was utilized, where the left ventricular walls and the two papillary muscles are visualized: the anterolateral and posteromedial papillary muscles. A true short-axis cross section of the left ventricle is confirmed when the two papillary muscles are approximately of equal size. The primary diagnostic goals of the transgastric midpapillary view are assessment of left ventricular systolic function, left ventricular volume, and regional wall motion.

However, the midesophageal four-chamber view could have been still used in this case as well. Midesophageal four-chamber is considered one of the most diagnostically valuable views in TEE, as it evaluates the chamber size and function, valvular function (both mitral and tricuspid), and regional motion of septal and lateral walls of the left ventricle [10].

Given the evidence showing harm from synthetic starch-based colloids, we used 5% albumin as the primary colloid in the event of acute blood loss or acute hypovolemia diagnosed.

The total fluid received was 3000 ml normal saline, 5000 ml lactated Ringer's, 1500 ml 5% albumin, 2900 PRBCs, four units fresh frozen plasma (FFP), and two sets of platelets for a 10-hour surgery. The estimated blood loss was 4000 ml. Urine output was 1800 ml.

Thromboelastogram was used intraoperatively to guide the transfusion of FFP and platelets. At the end of the case, the thromboelastogram numbers were in the normal ranges.

Postoperative Management

The patient was transferred intubated to the ICU at the end of the surgery on norepinephrine (5 mcg/min), propofol, and ketamine infusions. Fluid management continued with lactated Ringer's and the transfusion of blood, FFP, and platelets as needed—guided by the goal of achieving optimal volume status, hemodynamics, and electrolyte status. The hematocrit level was maintained above ~28–30, and coagulation profile and platelets were maintained above normal numbers.

On postoperative day 2, the patient was weaned off norepinephrine infusion and extubated. An epidural was placed in the ICU after the coagulation and platelets were in normal ranges.

Discussion

Perioperative fluid management is challenging in high-risk surgical patients. The aim of volume therapy is not only to prevent hypovolemia but also to reduce the risk of fluid overload. Hypovolemia is recognized as a risk factor for adverse effects, ranging from minor organ dysfunction to multiple organ failure and even death. Conversely, fluid overload may impair pulmonary, cardiac, and gastrointestinal functions, contributing to postoperative complications and a prolonged recovery. Therefore, appropriate hemodynamic monitoring is important for intraoperative fluid management [11].

TEE analysis based on the close approximation of the papillary muscles in the transgastric midpapillary view (TG Mid SAX) allows for a rapid qualitative assessment of ventricular filling so that fluids can be adjusted for the desired preload [12]. Figure 20.1 shows the list of the 11 views suggested by the American Society of Echocardiography and Society of Cardiovascular Anesthesiologists guidelines on basic perioperative TEE [13].

The filling pressures (i.e., central venous pressure and pulmonary artery occlusion pressure), as indirect indicators of filling volumes, have been the "standard" methods for decades, but, following significant criticism, volumetric measurements are now preferred [14]. The most commonly used parameters for left ventricular

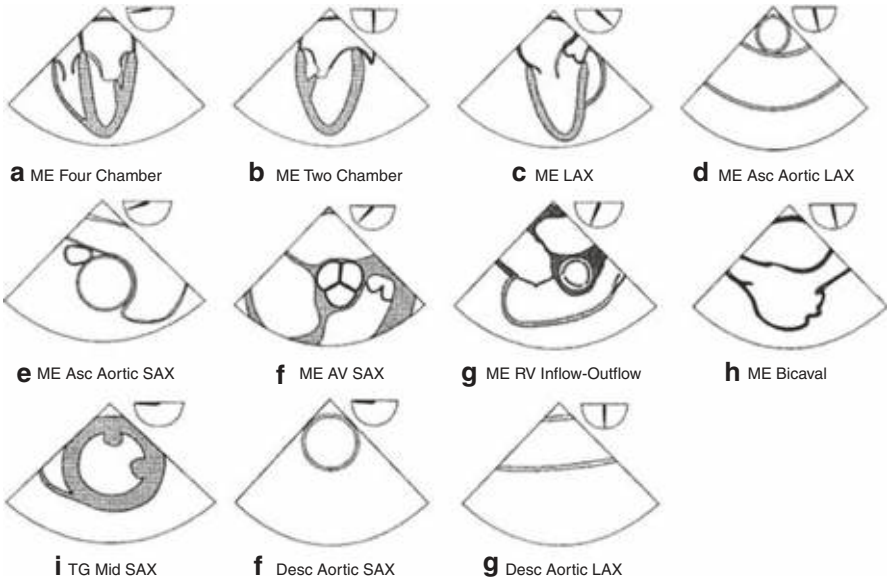

Fig. 20.1 List of the 11 views suggested by the American Society of Echocardiography and Society of Cardiovascular Anesthesiologists guidelines on basic perioperative transesophageal echocardiography. *ME* midesophageal, *LAX* long-axis view (Reprinted with permission from Reeves et al. [13])

preload assessment are the left ventricular end-diastolic diameter (LVEDD) and the left ventricular end-diastolic area (LVEDA), both obtained in the TG Mid SAX view [13].

In the clinical setting, SV is an important parameter of cardiac performance. Assessment of cardiac output (CO) is an important measure of responses to medical and surgical therapies, such as administration of inotropic agents to treat right and left heart failure. SV and CO are most reliably and easily measured at the left ventricular outflow tract (LVOT) [15].

The TEE-derived CO can be calculated as the product of SV and heart rate, where left ventricular SV is calculated by multiplying the time–velocity integral at the LVOT by the LVOT area. It is important to remember that area and flow measurements must be made at the same anatomical site. This calculation assumes that flow is laminar (i.e., not turbulent) and that the conduit being measured is an unchanging circular orifice such that it has the area of πr^2.

Stroke volume measured at LVOT level is simplified by the following equation:

$$\mathrm{SV} = \mathrm{VTI} \times \mathrm{CSA}_{\mathrm{LVOT}}$$

where CSA is the cross-sectional area, and VTI is the velocity–time integral.

The CSA (LVOT) is calculated from the LVOT diameter as follows:

$$\mathrm{CSA}_{\mathrm{LVOT}} = 0.785 \times \mathrm{diameter}^2$$

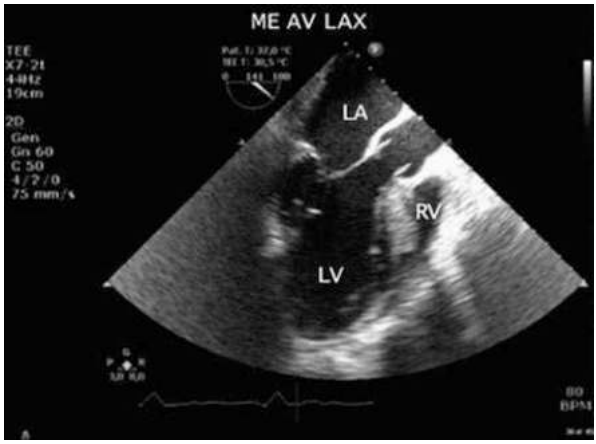

Fig. 20.2 Transoesophageal echocardiography view (midesophageal long-axis view) used to measure left ventricular outflow tract diameter usually best imaged at a multiplane angle of 110–140°. *AV* aortic valve, *LA* left atrium, *LV* left ventricle, *RV* right ventricle, *ME AV LAX* midesophageal aortic valve long-axis view (Modified with permission from Møller-Sørensen et al. [16])

The CSA of the LVOT is usually obtained from the midesophageal long axis (ME LAX) view at 110–140° (Fig. 20.2) [16]. Errors in diameter measurements are quadrupled, because the formula requires squaring the diameter. Therefore, very small errors in measurement make a dramatic difference to the calculation.

The diameter should be measured multiple times (usually 3) at midsystole in the midesophageal aortic valve long-axis (ME AV LAX) view, using the inner edge to inner edge technique, and then averaged. This measurement assumes that the annular size does not vary much throughout the cardiac cycle so the timing of this measurement is not crucial.

VTI measured at the level of the LVOT using pulse wave (PW) Doppler requires the sample volume to be positioned in the LVOT just proximal to the aortic valve. Because the blood flow is nearly parallel to the ultrasound beam, the best transesophageal views for this measurement are the transgastric long-axis (TG LAX) and the deep transgastric long-axis (deep TG LAX) views with PW Doppler sample volume placed in the LVOT (Fig. 20.3) [12, 16, 17].

Much controversy exists about the role of crystalloids and colloids in fluid therapy. Crystalloid salt solutions are the most commonly used fluids as they are available, inexpensive and non toxic. Crystalloid solutions start to leave the intravascular space within minutes, thereafter providing little hemodynamic support. Crystalloids accumulate in tissues including lungs and incision sites, thus promoting edema, weight gain and prolonged recovery [18, 19].

In Contrast, colloids remain in the circulation for hours, achieving better hemodynamic stability. Albumin has been used since the 1940s but it is expensive [19].

Proponents of colloid fluid point out that resuscitation with crystalloid solution dilutes the plasma proteins, with a subsequent reduction of plasma oncotic pressure resulting in fluid filtration from the intravascular to the interstitial compartment and the development of interstitial pulmonary edema. Proponents of crystalloid solutions have argued that albumin molecules normally enter the pulmonary interstitial compartment freely and then are cleared through the lymphatic system returning to the systemic circulation [20].

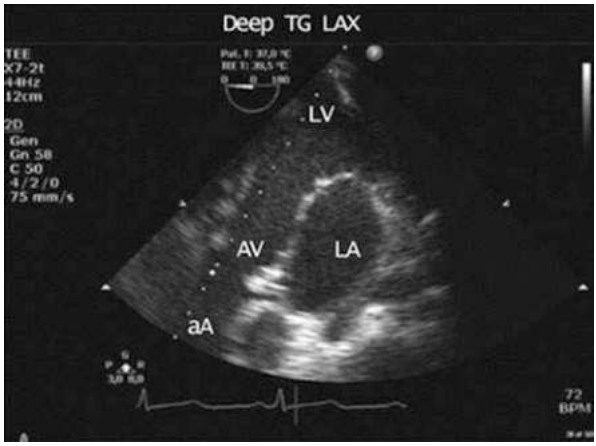

Fig. 20.3 Transoesophageal echocardiography view (deep transgastric long-axis view), used to measure velocity–time integral. *AV* aortic valve, *LA* left atrium, *LV* left ventricle, *aA* ascending aorta, *TG LAX* transgastric long-axis view (Modified with permission from Møller-Sørensen et al. [16])

Having enough venous access, with the availability of rapid infuser in the room and with the use of TEE translates to better management and ultimately better outcomes for our patients, especially the critically ill undergoing major orthopedic surgeries with the potential of massive blood loss.

Future use of technologies to anticipate and reduce intraoperative hypotensive periods would improve patient outcomes after surgeries. For example the use of Hypotension Prediction Index that is derived from arterial waveforms and predicts hypotension, and the software that also provides advanced hemodynamic data including cardiac output, vascular elastance, and stroke volume would guide anesthesiologists to manage patients undergoing major orthopedic surgeries where the use of Transesophageal echocardiography would be contraindicated [21].

Conclusion

Fluid management is crucial with significant effect on morbidity and mortality in major orthopedic surgery. Intravenous fluid is given during the surgery to maintain *intravascular volume* and *tissue perfusion*. The patient loses fluids through multiple mechanisms—insensible loss, urine output, third spacing, and blood loss. Replacement of conventional third spacing is debatable. We should replace fluids carefully examining the blood loss and urine output. Transesophageal echocardiography can be utilized, especially in our critically ill patients, to avoid tissue underperfusion and edema in major orthopedic surgeries when we are expecting significant blood loss. TEE has evolved as an important diagnostic tool outside the field of cardiac anesthesia, and it has gained increasing importance in managing sicker patients undergoing major orthopedic surgeries with the potential of massive bleeding.

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Case Scenario for Perioperative Fluid Management for Major Colorectal Surgery

21

Kamal Maheshwari

Abstract

The goal of perioperative fluid management is to maintain intravascular volume, safeguard adequate perfusion of vital organs—brain, heart, kidney, and gut—and maintain acid–base and electrolytes balance. Mostly, clinicians use prior experience and rule based approach to manage perioperative fluid administration which leads to wide variation in clinical practice and outcomes. A data driven goal-directed approach is needed. Individualized fluid management guided by patient factors, surgical factors and advacned hemodynmaic parameters can help improve outcomes.

Introduction

The goal of perioperative fluid management is to maintain intravascular volume, safeguard adequate perfusion of vital organs (brain, heart, kidney, and gut), and maintain acid–base and electrolytes balance [1]. The three important questions a clinicians needs to answer is when to give fluids, which type of fluid and how much? The conventional approach, primarily based on prior experience and set rules formulas leads to wide variation in clinical practice and outcomes. Also, just restricting fluids is not safe. In major abdominal surgery patients a restrictive fluid regimen was not associated with a higher rate of disability-free survival than a liberal fluid regimen and was associated with a higher rate of acute kidney injury. (PMID: 29742967) Therefore, a detailed understanding of cardiovascular physiology and the complex interaction between stressed and unstressed intravascular volume is the key in making right decision. (PMID 2925606). Advanced hemodynamic parameters like

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stroke volume, stroke volume variation which help by setting patient specific goals for fluid management thus helps clinical decision making.

Various stressors—preoperative fasting, neurohormonal changes, and pain—augment the surgical stress response, eventually affecting fluid management. In the preoperative phase, data suggests that avoidance of preoperative bowel preparation and avoidance of undue preoperative dehydration can improve outcomes. In addition, the type—crystalloid vs. colloid or balanced vs. unbalanced fluid—of intraoperative fluid may influence patient outcomes. For example, in abdominal surgery patients intraoperative hydroxyethyl starch administration did not reduce serious complications, compared to lactated Ringer's. (PMID: 30882476) In other words, colloids are expensive and should be avoided. The role of goal-directed therapy (GDT) using dynamic hemodynamic monitors is evolving, but the data do suggest improved patient outcomes. (PMID: 24842135) The hetergenity in the outcome benefit with the use for GDT is due to the difference in protcols, hemodynamic parameter and the surgical setting. In the postoperative period, a fluid-restrictive regimen coupled with early enteral feeding also seems to result in improved patient outcomes [2].

Enhanced Recovery After Surgery

Optimal fluid therapy and goal-directed therapy are important components of fast-track surgery: Enhanced Recovery After Surgery (ERAS) Program [3]. The ERAS protocol has various preoperative, intraoperative, and postoperative components (Fig. 21.1) [5, 6]. In 2012, Gustafsson et al. published ERAS Society recommendations for perioperative care in elective colonic surgery [7]. The fluid management can also impact the incidence of postoperative ileus (POI). Prevention of POI is paramount to improve patient comfort and to reduce the length of stay (LOS) and cost of care. Multiple strategies have been used to facilitate gastrointestinal recovery (Table 21.1) [8].

Fluid Management

Postoperative complications are common [9, 10], and reducing complications thus decreases both cost and mortality [11]. Optimal fluid management may help reduce these complications, but nonetheless requires defining when to give intravenous (IV) fluid, what kind of IV fluid (colloid or crystalloid), and how much to administer [12]. *Which* fluid to use for resuscitation crystalloid and colloid is a challenging question, and current evidence remains inconclusive. For example, 90-day mortality is similar in critical care patients resuscitated with 6% hydroxyethyl starch (130/0.4) or saline [13, 14]. *When* to give fluid or to assess fluid responsiveness is a more difficult question—one potentially addressed by using measures of cardiac output and hemodynamic responsiveness to guide the *timing and amount* of fluid given.

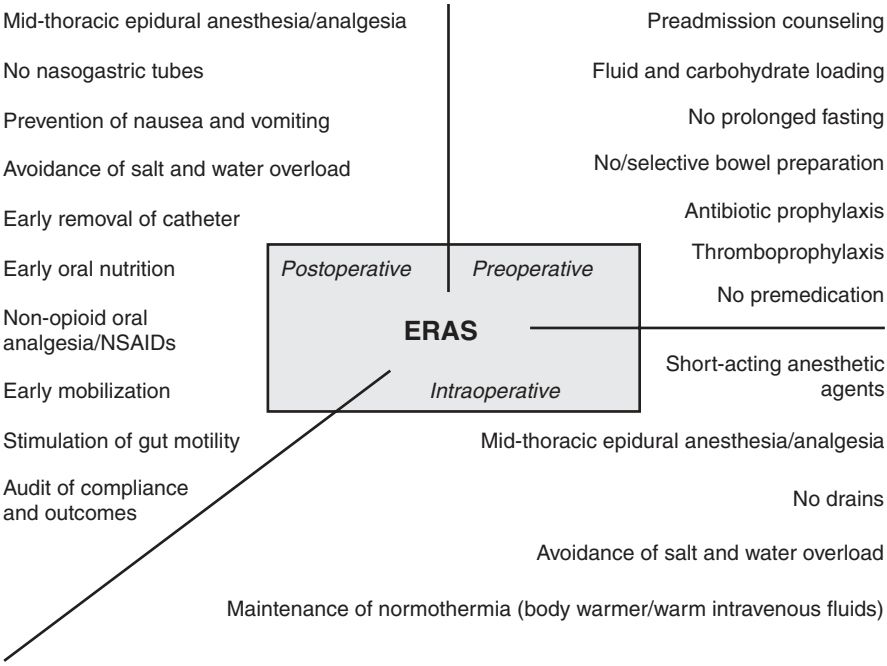

Fig. 21.1 Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery: pathophysiological considerations (Modified with permission from Varadhan et al. [4])

Table 21.1 Strategies to prevent postoperative ileus

Intervention	Mechanism	Benefit
Salt and fluid overload	↓ gut edema and stretch	++
Carbohydrate loading	↓ insulin resistance	±
Routine nasogastric tubes	Prophylactic drainage of stomach	–
Intravenous lidocaine	Anti-inflammatory; opioid-sparing	+
Coffee	Stimulatory effect	+
Chewing gum	Stimulatory effect	+
NSAIDs	Opioid sparing; anti-inflammatory	++
Early enteral nutrition	Anabolic; ↓ insulin resistance; stimulatory	++
ERPs	Multimodal effect	++
Laparoscopic surgery	↓ tissue trauma; ↓ bowel handling; ↓ inflammatory reaction	++
Alvimopan	μ-Opioid receptor antagonist	++
Midthoracic epidural anesthesia	↓ inflammatory response ↓ sympathetic stimulation ↓ opioid requirement	++
Early mobilization	? Anabolic effect	+/±
Nicotine	Colonic prokinetic	+
Daikenchuto	Anti-inflammatory on acetylcholine receptors	+
Magnesium sulfate	Anesthetic effect	+
Prokinetics	Prokinetic effect	±

Reprinted with permission from Bragg et al. [8]
NSAIDs nonsteroidal anti-inflammatory drugs, *ERPs* enhanced recovery programs
++ definite benefit, + possible benefit, ± no benefit, – possible harm

Goal-Directed Therapy

Fluid responsiveness is defined by the stroke volume increase in response to a fluid bolus and is the basis for goal-directed therapy (GDT) [15]. GDT is among the protocol-based strategies for optimizing fluid management and has been shown to reduce hospital length of stay and complication rates in various surgical settings [16, 17]. GDT has also been shown to be cost-effective and results in better clinical outcomes in high-risk surgical patients [18]. GDT reduces mortality most in patients undergoing high-risk surgery (>20% mortality), although complication rates are reduced in all surgical groups [9].

Advanced Hemodynamic Monitoring.

Various invasive and noninvasive monitors are available to provide objective estimates of stroke volume or cardiac output, which is the basis for GDT. Invasive monitors include pulmonary artery catheters (PAC), arterial catheters, and central venous catheters. Noninvasive monitors include PiCCO (PULSION Medical Systems, Feldkirchen, Germany) [19], LiDCO (LiDCO Ltd., London, UK) [20], NICOM (Cheetah Medical, Tel Aviv, Israel) [15, 19], Flotrac (Edwards Lifesciences, Irvine, CA, USA) [21, 22], and NexFin (BMEYE, Amsterdam, The Netherlands) [23, 24], which variously provide estimates of stroke volume or cardiac output.

GDT, using PVI (Pleth variability index), reduces intraoperative fluid administration and reduces intraoperative and postoperative lactate concentrations [25]. A bioreactance-based system, NICOM, is sensitive and specific in predicting cardiac output changes (0.91 and 0.95, respectively), compared to Flotrac (0.86 and 0.92, respectively) in cardiac surgery patients [26]. The NexFin monitor is based on a volume clamp method applied to a finger and generates a noninvasive arterial waveform, which in turn can be used to estimate cardiac output [27, 28]. NexFin accurately estimates blood pressure [29] and cardiac output in healthy adults [27, 30], but whether using the system reduces complications remains unknown [31].

In addition to PA catheters, monitors that require an arterial catheter include PiCCO, Vigileo (Edwards Lifesciences, Irvine, CA, USA), and LiDCO. PiCCO uses pulse contour technology, along with transpulmonary thermodilution, to provide reliable estimates of cardiac output [19]. Stroke volume measured by the Vigileo monitor correlates somewhat with the transthoracic echocardiogram (r^2 = 0.56) in spontaneously breathing individuals during passive leg raising [32]. The Flotrac software has been updated multiple times (now Flotrac 3) and has been validated in septic patients with low systemic vascular resistance (SVR) [33]. It has been used to guide fluid resuscitation in burn patients, which reduced fluid administration compared to routine management while maintaining similar urine output (0.8 ml/kg/h) [34]. Other LiDCO-based studies are in progress [35].

Evidence for GDT

Numerous studies demonstrate that GDT reduces complications, infections, and the duration of hospitalization [36]. Results are generally similar, even though devices and protocols differ [37–39]. For example, Benes et al. used colloid and dobutamine infusion to optimize cardiac index and stroke volume variation in a high-risk elective abdominal surgery group and reported a 56% reduction in 30-day postoperative complications along with a 10% reduction in hospital LOS [37]. In a quality improvement study by NHS/NICE (National Health Service/National Institute for Health and Care Excellence, UK), there was a 27% decrease in hospital length of stay, equivalent to 3.5 days, across all specialties [40]. Esophageal Doppler has been successfully used to measure cardiac output and stroke volume [41–48]. In a randomized, single-blind trial evaluating patients having major operations, Ramsingh et al. reported a faster return of gastrointestinal function (3 vs. 4 days), faster return to oral nutrition (4 vs. 5 days), and a 2.5-day (33%) decrease in hospital length of stay. GDT has also been shown to be cost-effective and clinically helpful in postoperative patients [18].

In contrast, there are studies that showed no benefit of GDT. In a pragmatic, multicenter, randomized, observer-blind trial involving 734 patients, Pearse et al. observed no significant reduction in postoperative complication (relative risk, 0.84; 95% CI: 0.71–1.01) and no significant reduction in hospital LOS [17]. Early GDT also failed to improve outcomes in patients with early septic shock [49]. Nonetheless, most studies do report benefit from GDT, and the major ones are summarized in Table 21.2 [17, 37, 38, 40, 50–52].

Table 21.2 Evidence for perioperative goal-directed therapy

	Study design	Equipment	Parameter	Fluid	Outcomes
Donati [50]	RCT	CVP and oxygen extraction	DO_2	Colloid	60% decrease in postoperative complications 16% decrease in LOS
Benes [37]	RCT	Vigileo/ FloTrac system	SVV	Colloid	56% reduction in 30-day postoperative complications 10% reduction in LOS
Cecconi [38]	RCT	Vigileo/ FloTrac system	SV	Colloid	20% reduction in postoperative complications
Kuper (NHS) [40]	Before/after comparison	Esophageal Doppler	SV	Crystalloid/ colloid	25% decrease in LOS (3.7 days decrease)
Wang [51]	RCT	Vigileo/ FloTrac system	SVV	Crystalloid/ colloid	19% decrease in LOS

(continued)

Table 21.2 (continued)

	Study design	Equipment	Parameter	Fluid	Outcomes
Ramsingh [52]	RCT	Vigileo/ FloTrac system	SVV	Colloid	33% decrease in LOS (2.5 days decrease)
Pearse et al. (2014) [17]	Pragmatic, randomized, observer-blinded trial	LiDCO rapid, LiDCO ltd	SV	Colloid	No significant reduction of postoperative complications No significant reduction in LOS

RCT randomized controlled trial, *CVP* central venous pressure, DO_2 oxygen delivery, *LOS* length of stay, *SVV* stroke volume variation, *SV* stroke volume

One of the challenge in the GDT protocols is the protocol adherence. There is still subjectivity involved in the data interpretation and fluid administration. To some extent, adherence can be improved with use of closed loop technology. For example, Joosten et al. successfully used closed-loop assisted goal-directed fluid therapy in major abdominal surgery. (PMID: 2906883) New algorithms like Assited Fluid Management are being evaluated to help simplify the fluid management. ClinicalTrials.gov Identifier: NCT03469570.

Case History

An 82-year-old female, American Society of Anesthesiologists (ASA) status 4, is scheduled for open abdominoperineal excision with an end colostomy. Her functional class is III. The past medical history is significant of:

1. Congestive heart failure—compensated, ejection fraction = 68 ± 5%
2. Atrial fibrillation—on Diltiazem for rate control
3. Hypertension—on furosemide
4. Hyperlipidemia—on simvastatin
5. Chronic obstructive pulmonary disease—on 2-l nasal cannula oxygen as needed—stable
6. Diabetes mellitus—on Aspart insulin and Lantus insulin, HbA1C 8.1
7. Rheumatoid arthritis—on prednisone
8. Rectal cancer—s/p chemotherapy and radiation therapy

Preoperative vitals: blood pressure (BP), 159/76 mmHg; pulse, 78; height, 147.3 cm (4′ 9.99″);l weight, 60.1 kg (132 lb. 7.9 oz); body mass index (BMI), 27.70 kg/m^2; SpO_2, 96%.

Preoperative Management

The patient received an education session on the expected course of the perioperative period, especially regarding colostomy management, pain management, and duration of hospitalization. No bowel preparation was ordered. The patient was allowed to drink clear liquids up to 2 h before surgery. She was also given a complex carbohydrate fluid to be used overnight and advised to stop drinking this fluid up to 2 h before surgery. The goal is to minimize the period of fasting and dehydration. In the preoperative area, an 18-gauge peripheral intravenous line was placed, and a balanced crystalloid fluid lactated Ringer's was started at 2 ml/kg/h. The patient received no sedation and anxiolysis, and the preoperative teaching including expectations regarding pain, diet, and physical therapy was completed.

Intraoperative Management

The patient was transferred to the operating room where all the team members introduced themselves and their roles. According to the safe surgery checklist, a preoperative sign-in was performed.

Monitoring

The patient was monitored according to standards set by the American Society of Anesthesiologists (electrocardiogram, noninvasive blood pressure, oxygen saturation, temperature). An epidural catheter was inserted for perioperative analgesia in the sitting position. Anesthesia was induced with propofol (1–2 mg/kg), rocuronium (0.6 mg/kg), and fentanyl (1–2 μg/kg). An arterial line was placed for perioperative hemodynamic management. Another peripheral intravenous line (16-gauge) was placed for fluid management.

Maintenance

Anesthesia was subsequently maintained with sevoflurane (up to 1.2 MAC) in a carrier gas of 50–80% inspired oxygen and air. An intermittent bolus of fentanyl was administered according to the patient's requirements, although epidural was used for primary pain management during the surgical case. After induction of anesthesia, the epidural medication (0.125% bupivacaine) was started at 5 ml/h.

An additional muscle relaxant was given as necessary to maintain one to two mechanical twitches in response to supramaximal stimulation (train-of-four stimulation) of the ulnar nerve at the wrist. Ventilation was controlled to maintain

end-tidal carbon dioxide tension near 35 mmHg. The tidal volume was set between 8 and 10 ml/kg lean body weight to keep the peak inspiratory pressure below 30 mmHg, and a positive end-expiratory pressure of 5 mmHg was administered. The temperature was monitored, and normothermia (core temperature > 36 °C) was maintained with forced-air warming.

Fluid and Hemodynamic Management

Preoperative overnight fasting may instinctively seem to affect intravascular volume. But, in fact, the functional intravascular volume is minimally affected by preoperative fasting [53, 54].

The patients will be given 3 ml/kg/h crystalloid for maintenance normalized to ideal body weight, 80 kg. (Men: ideal body weight [in kilograms] = 52 kg + 1.9 kg for every 2.5 cm over 150 cm; Women: ideal body weight [in kilograms] = 49 kg + 1.7 kg for every 2.5 cm over 150 cm).

Although any of the commercially available cardiac output monitoring devices—as previously described—can be used, we used the Flotrac system. The goal-directed fluid therapy will be guided by stroke volume derived from the Flotrac system (Fig. 21.2). The dynamic parameters can also be used, but they are predisposed to error in the presence of cardiac arrhythmias and are valid only for mechanically ventilated patients with 8–10 ml/kg tidal volume.

Given the evidence showing harm from synthetic starch-based colloids, we used 5% albumin as the primary colloid in the event of acute blood loss or acute hypovolemia diagnosed.

This patient received three boluses over the period of the surgery in addition to the maintenance fluid. The total fluid received was 1750 ml for a 5-hour surgery. The blood loss was 200 ml.

The patient remained in atrial fibrillation throughout the case with HR < 100 beats per minute. The blood glucose was measured periodically and treated with regular insulin with the goal of <200 mg/dl.

Postoperative Management

The patient was extubated at the end of the surgery in the operating room. Epidural medication provided good pain relief. Fluid management continued with lactated Ringer's at 1 ml/kg/h and was guided by the goal of achieving optimal volume status, hemodynamics, and electrolyte status.

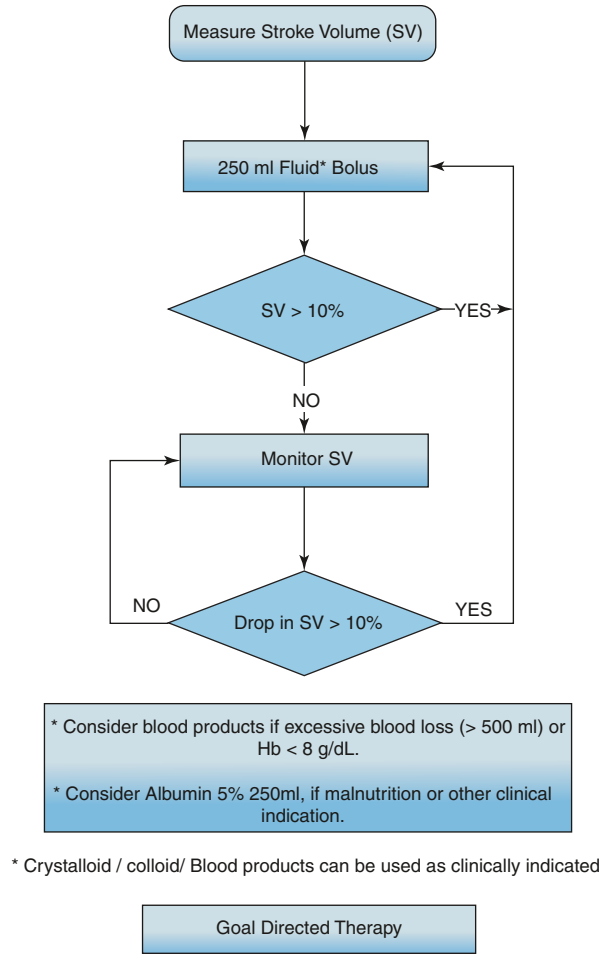

Fig. 21.2 Goal-directed fluid therapy algorithm

Discussion

Individuals differ in their response to surgical stress. The age, functional status, and comorbidities make them prone to postoperative complications and mortality [10, 55, 56]. Risk factors such as obesity, smoking, alcohol, anemia, and poor nutritional status are the modifiable factors that can influence perioperative outcomes such as cardiopulmonary complications and infections. Efforts should be made to optimize all the comorbid conditions and reduce risk factors before going for surgery. For example, smoking cessation programs are not only important for patient health but also an important quality-of-care metric influencing payments in the United States [57, 58].

Preoperative assessment of functional capacity using the invasive or noninvasive test as guided by the history and physical exam should be performed. Cardiac stress testing and 6-minute walking distance (6 MWD) are two examples; 6 MWD < 350 m predicts mortality after surgery [59]. Lee et al. measured the distance 112 patients walked in 6 min the week before scheduled resection of benign or malignant colorectal disease and concluded that the distance walked in 6 min before surgery can predict postoperative complications in patients undergoing colorectal surgery [60].

The ERAS program has been shown to be effective in improving the quality of care and patient safety in colorectal surgery. Patient education is an important component of the ERAS program. In a review of the ERAS program for gastrointestinal surgery, Scott et al. noted, "The whole patient journey, starting with evaluation, then optimization of physical, mental, nutritional functions (prehabilitation), then moving through surgery and the hospital episode and finishing with recovery, should be explained well in advance to facilitate active participation, comprehension and allay anxiety" [5].

Fluid management is another important component with a significant effect on morbidity and mortality in colorectal surgery. Intravenous fluid is given during the surgery to maintain *intravascular volume* and *tissue perfusion*. The ultimate goal is to provide oxygen and essential nutrients to the tissue and to remove waste material from the tissues. To maintain intravascular volume during the surgery, the fluid losses have to be replaced by appropriate fluid. The patient loses fluids through multiple mechanisms: insensible loss, urine output, third spacing, and blood loss. Replacement of conventional third spacing is not recommended, and Chappell et al. questioned the existence of the third space [61]. Furthermore, the insensible losses are very minuscule. Consequently, we should replace fluids carefully examining the blood loss and urine output. Overzealous fluid replacement—algorithm-based approaches—may result in acute hypervolemia, which can actually damage vascular endothelin glycocalyx, emphasizing the appropriate use of fluids.

With regard to the tissue perfusion in colorectal surgery, the blood flow to the colon is poorly autoregulated and is primarily dependent on mean arterial pressure and to a lesser extent on the cardiac output [62, 63]. To maintain colonic perfusion, adequate mean arterial pressure should be maintained.

Fluid responsiveness is defined by the stroke volume increase in response to a fluid bolus and is the basis for goal-directed therapy [15]. GDT is among the protocol-based strategies for optimizing fluid management and has been shown to reduce hospital LOS and complication rates in various surgical settings [16, 17]. GDT has also been shown to be cost-effective and result in better clinical outcomes in high-risk surgical patients [18]. GDT reduces mortality mostly in patients undergoing high-risk surgery (>20% mortality), although complication rates are reduced in all surgical groups [9].

The GDT can help decide when to give IV fluids and how much. On the other hand, the type of IV fluid (colloid or crystalloid, balanced or unbalanced) use for resuscitation is a challenging question, and current evidence remains inconclusive [12]. However, we recommend using balanced crystalloid for replacement during surgery and limiting colloid use for acute hypovolemia.

Conclusion

Optimal fluid therapy and goal-directed therapy are important components of fast-track surgery/Enhanced Recovery After Surgery program. Individualized fluid management should be guided by patient factors, surgical factors and dynamic hemodynamic parameters,. Though high-quality evidence for use of GDT in fluid management is not available at this time, GDT may provide useful information for clinical decision making. In this case scenario, we utilized evidence-based best practices for fluid management in the perioperative period to improve the quality of care and patient safety. We limited the preoperative fasting, waived mechanical bowel prep, administered goal-directed fluids, used balanced fluid, and restricted colloid use.

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Case Scenario for Fluid Therapy in Septic Shock

22

Ashish K. Khanna, Michael D. Font, and Piyush Mathur

Abstract

Septic shock represents a profound systemic inflammatory derangement with components of functional hypovolemia, altered oxygen delivery, myocardial dysfunction, peripheral vasoplegia, and diffuse capillary leak. In this case scenario, a patient exhibits all of the aforementioned findings with lactic acidosis, elevated troponin, persistent hypotension despite vasopressor use, acute kidney injury, and acute lung injury due to septic shock. In addition to source control and early antibiotic administration, the goals of treatment are early and aggressive fluid resuscitation, maintenance of tissue perfusion, and judicious and balanced application of vasopressor support. As excess fluid balance is associated with worse outcomes, it is the job of the clinician to evaluate the patient's response to fluid therapy with one of several tools. After adequate fluid resuscitation has been achieved, additional support may be required with vasopressors. As the patient's clinical course improves the physician should aim to gently 'de-resuscitate' excess fluid.

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Key Points

1. The goals of resuscitation are to optimize cardiac output and tissue perfusion.
2. Early but judicious and multi-modal vasopressor use may help maintain perfusion pressure and obviate excessive administration of intravenous fluids.
3. Determining fluid responsiveness is a dynamic process that requires repeated assessment of cardiac performance.
4. Lactated Ringer's or Plasma-Lyte may be the optimum fluids for resuscitation.
5. Albumin use may have a particular niche for resuscitation utilization in sepsis and septic shock.
6. Critically ill patients with septic shock may be exquisitely sensitive to a drop in blood pressure.
7. Positive fluid balance has an adverse effect on outcomes including mortality in the intensive care unit (ICU).

Case Scenario

A 67-year-old previously healthy Caucasian male is admitted to the intensive care unit (ICU) with a diagnosis of septic shock due to necrotizing fasciitis of the right arm. He presented to the emergency department (ED) with a 3-day history of right upper extremity pain and swelling that rapidly progressed after experiencing a cut on his hand while gardening.

In the ED, he had altered mental status, tachycardia (heart rate > 100/min) and hypotension (Mean Arterial Pressure of 50-55 mmHg), moderate hypoxemia, and profound oliguria with a lactic acidosis (pH 7.09). He required intubation for airway protection for his acidosis and received broad-spectrum antibiotics, 3 L of 0.9% saline, and was placed on a norepinephrine infusion at 0.05 mcg/kg/min en route to the operating suite for urgent debridement.

He arrived in the intensive care unit 2 h after undergoing wide debridement and forearm fasciotomies, and having received 5 more liters of 0.9% sodium chloride and 25 g of 5% albumin solution in the operating room (OR). Upon arrival to the ICU, he is intubated and sedated with his right upper extremity heavily bandaged but with modest soakage of serosanguinous fluid.

Admission vital signs: blood pressure (BP), 85/38 mmHg; heart rate, 134/min; SaO_2, 92% (FiO_2, 60%); respiratory rate, 16 on ventilator (Assist control); temperature, 35.7 °C; central venous pressure (CVP), 9 mmHg. Chestradiography shows bilateralpatchybilateralinfiltrates.

Laboratory data:

- Arterial blood gas: pO_2 64, pCO_2 46, pH 7.15 bicarbonate 15 mEq/l, lactate 6.8 mEq/l, base deficit (−9)
- Electrolytes: sodium 144 mEq/l, potassium 3.9 mEq/l bicarbonate 14 mEq/l, chloride 114 mEq/l, BUN 26 mg/dl, creatinine 2.1 mg/dl, troponin T 0.053 (↑)

- Complete blood count: WBC 24,000/mm^3; 90% PMNs hemoglobin 11 gm/dl, hematocrit 34%, platelet count 124,000/mm^3
- Electrocardiogram (EKG)—sinus tachycardia with nonspecific ST and T wave changes.

Upon arrival to the ICU, an ultrasound is used to assess his IVC collapsibility, which shows a 40% increase in diameter with inspiration. His intravenous fluids are changed to lactated Ringer's (LR), he receives boluses totaling 30 ml/kg and is started on an infusion of 200 ml/h. His norepinephrine is increased to 0.1 mcg/kg/min, hydrocortisone is added and dosed at 50 mg q6hrs IV and vasopressin is added as an infusion of 0.04 units/h. Over the following hours, he continues to have hemodynamic instability. Repeat ultrasound shows minimal IVC variation with respiration, and Angiotensin II is initiated at 20 ng/kg/min. Bedside echocardiography with volume-time-integral (VTI) reveals normal heart function with cardiac index (CI) of 3.5 L/min/m^2. Periodic IVC assessment is repeated concurrently with measurements of serum lactate, and vasopressors are titrated with bolus fluid administration to maintain (CI) > 2 L/min/m^2 and a mean arterial pressure (MAP) > 65 mmHg.

Over the ensuing 24 h, albumin is chosen for subsequent fluid boluses in increments of 25 g each, and each infused over a period of 2 h. Two units of packed red blood cells (PRBCs) are also administered for a fall in his hemoglobin to 7.0 g/dl with a concurrent serum lactate level of 5.2 mEq/L.

The patient required two subsequent trips to the operating room for debridement, but at the 72-hour mark had stabilized markedly with discontinuation of his vasopressors, and a fall in his creatinine to 1.4 mg/dL. Judicious diuresis was initiated on ICU day number 3, guided by ongoing continuous assessment of cardiac index (CI),periodic ultrasonographic assessment of his IVC, and PaO2/FiO2 ratio on the mechanical ventilator.

He was able to be extubated on ICU day number 6 with, at that time, an overall positive fluid balance of 4 L.

Discussion

Septic shock represents a profound systemic inflammatory derangement with components of functional hypovolemia, altered oxygen delivery, myocardial dysfunction, peripheral vasoplegia, and diffuse capillary leak [1]. The latest revision of the definition of septic shock defines this entity as a subset of sepsis associated with profound circulatory, cellular, and metabolic abnormalities & greater risk of mortality than with sepsis alone [2]. A clinical definition uses criteria of vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or higher and a serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. Our patient exhibited all of the aforementioned findings with lactic acidosis, elevated troponin, persistent hypotension despite vasopressor use, acute kidney injury, and pneumonitis presumably from his sepsis.

In addition to source control and early antibiotic administration, a cornerstone of therapy is the maintenance of tissue perfusion via early and aggressive fluid resuscitation and judicious application of vasopressor support [3, 4]. In the early 2000's a landmark trial showed the benefit of "early goal-directed therapy" (EGDT), which consisted several resuscitation goals including CVP 8–12 mm Hg, MAP >65%, and SvO2 > 70% which were achieved by fluids, vasopressors, blood transfusions, and inotropes as needed [5]. This strategy of aggressive fluid resuscitation (in addition to vasopressors, steroids, and timed antibiotic administration)was incorporated into the guidelines of the Surviving Sepsis Campaign and was widely adopted [6, 7]. However, several subsequent trials and meta-analyses failed to replicate the survival benefits of EGDT. Most recently, the Protocolized Care for Early Septic Shock (PROCESS), Australasian Resuscitation in Sepsis Evaluation (ARISE), and Protocolised Management in Sepsis (ProMISe) trials all failed to demonstrate survival benefit from a protocol-driven resuscitation scheme, though these later studies had different rates of early antibiotic usage and central venous line placement from earlier studies [8–10].

Despite this, several components of EGDT continue to be endorsed by the Surviving Sepsis Campaign guidelines, including aggressive fluid resuscitation in all septic patients, and the early administration of antibiotics within 1 h of suspicion of sepsis [11, 12]. While there is some concern regarding the over-application of antibiotics with a 1-h mandate [13], there is retrospective data to suggest that the early administration of antibiotics reduces mortality in septic patients [14]. Furthermore, it has been postulated that bundle implementation, as mandated by the Center for Medicare and Medicaid Services(CMS), may improve survival [15, 16]. In our patient, septic shock resuscitation started in the operative room. There have been efforts to apply goal-directed fluid management to optimize intraoperative cardiac output, mostly by measuring volume responsiveness and administering fluids, vasopressors, or inotropes accordingly. There has have been many such proposed protocols, however the surgical populations and optimization protocols are heterogenous, and data have shown inconsistent reductions in mortality [17–19]. Regardless, it is prudent to thoughtfully administer fluids only in the context of suspected hypovolemia, and to quickly support MAP goals with vasopressors or inotropes if the patients does not show signs of volume responsiveness.

Our patient was initiated on early broad spectrum antibiotics, though an ongoing challenge is the identification of a true 'hour zero' for when this septic insult first started. In this context, by the time an average patient reaches the emergency room, ICU or operating room, most providers are playing catch-up in terms of timely and appropriate interventions.

Fluid resuscitation strategies are based on the premise that regardless of fluid type, as with antibiotic administration, early resuscitation decreases mortality by halting the amount and the duration of hypotension [20].

Though traditional goals of resuscitation target a MAP of at least 65 mmHg, recent work has shown that the critically ill population may be very sensitive to blood pressure fluctuations at MAPs higher than 65mmHg [21, 22]. Therefore, an appropriate, individualized MAP target (usually higher than 65 mmHg) should be

set early on in the management of resuscitation. In addition, the means to achieve a blood pressure target should be centered on early, and multi-modal use of vasopressors. This philosophy of broad spectrum vasopressors, stems from the deleterious effects of high dose catecholamine monotherapy [23, 24].

Guidelines recommend switching to additional epinephrine or vasopressin after a lack of effect of high dose norepinephrine is seen [25]. The advent of new and novel vasopressors such as Angiotensin II, has provided critical care practitioners a new tool in their armamentarium that allows a balanced approach with a decrease in maximum toxic doses of individual vasopressor classes [26]. We added both vasopressin and angiotensin II early on, and were able to effectively and efficiently reverse hypotension and its associated harm. Fluid resuscitation should continue as ongoing effort after the initial load. Despite the accepted 6-h window for lactate normalization, aggressive fluid resuscitation may benefit even if delayed as much as 24 h [27, 28]. Critical to successful fluid resuscitation is the ability to assess volume responsiveness (VR—an increase in cardiac index or performance with fluid administration) over time [29].

A confounding issue in the adoption of existing protocols is that clinical targets for achieving adequate volume expansion are potentially flawed. Static parameters of fluid responsiveness such as central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP), and left ventricular end-diastolic area (LVEDA) are poor predictors of fluid responsiveness, not only in septic patients but also in the perioperative setting [30–32].

The necessity to achieve "just adequate" rather than excess fluid balance is underscored by the strong association between positive fluid balance and increased mortality in the ICU population. Although spontaneous diuresis may occur post resuscitation in some patients, this diuresis may not happen in patients more predisposed to fluid accumulation [33, 34]. The persistence of a positive fluid balance over time is also strongly associated with increased mortality in septic patients with a hazard ratio of 1.014 per mL/kg increase in positive fluid balance [35]. Despite the very high resuscitation volume associated with the treatment of septic shock, the optimum fluid balance at the 12-h mark is suggested to be only 3 L [4]. In this example, we made efforts at judicious diuresis starting at ICU day 3, and guided our response using clinical, imaging and hemodynamic parameters. An important pearl is to make a switch from resuscitation to de-resuscitation as a step-wise process, and not go from aggressive fluid loading to unloading (diuresis) strategies without an intermediate period, where other phenomenon such as auto-diuresis, recovery from septic kidney injury and mobilization of extra vascular fluids could be working in the background.

Given the harm associated with over-resuscitation, there has been great interest in identifying reliable predictors of volume responsiveness to guide fluid therapy. Although the intial EGDT guidelines used CVP measurements as a proxy of volume status and volume responsiveness, the CVP has been shown repeatedly to be an unreliable predictor of a patient's volume responsiveness, and should not be used to make decisions about fluid therapy [36–39]. The exception to this rule is the case of very low or very high CVP (<6 or >15 mmHg), in which case the majority of

patients are responsive and non-responsive, accordingly [40]. Likewise, the static inferior vena cava (IVC) size determined by ultrasonography is a reflection of CVP, and therefore is a poor predictor of volume responsiveness [41].

There are several ways of using ultrasonography and echocardiography to predict fluid responsiveness. The first of these are 'static' measurements, that is measurements of the patient's physiology without introducing a change in volume. The assessment of IVC diameter variation with respiration has been shown to be an accurate predictor of volume responders among intubated patients, however this has limited predictive ability and should be used with caution in spontaneously ventilating patients [42, 43]. Superior vena cava (SVC) collapsibility measured via transesophageal echocardiography (TEE) has excellent sensitivity and specificity to identify volume responders [44]. Measurement of right internal jugular distensibility has also been suggested as a potential surrogate marker for IVC assessment [45]. The measure of respiratory variations of aortic flow by the volume-time-integral (VTI) measurement is the most accurate of the static methods [46].

The 'dynamic' assessments of volume responsiveness include measuring the cardiac output (CO) before and after a small fluid bolus, to predict the response to a larger bolus. The passive leg raise (PLR) test is a method of measuring CO via TTE before and after an auto-infusion of pooled venous blood from the patient's lower extremities to their heart. The PLR has been shown to be an accurate predictor of volume responsiveness in intubated and spontaneously breathing patients alike, however this can be a cumbersome test and can be limited by the patient's surgical sites [46–48]. The 'mini-fluid challenge' is similar test involving a small bolus (100-250 cc) of fluids over 1 minute, and assessing changes in CO. This test has been shown to have high sensitivity and specificity [49, 50].

It must be emphasized that with the above methods, merely watching for an increased arterial pressure is not adequate to measure volume responsiveness. The CO must be directly measured using either invasive (e.g. PA catheter) or noninvasive (TTE) means. The CO may be measured by the VTI method on TTE, which has been shown to correlate well with measurements derived from a PA catheter [51, 52].

More invasive means of predicting volume responsiveness using arterial waveform analysis include stroke volume variation SVV and pulse pressure variation (PPV). PPV has been shown to reasonably reflect volume responsiveness. A cutoff of >13% arterial waveform variability has been found to reliably represent associated decreased right ventricular preload at end inspiration with the resultant decreased left ventricular stroke volume [29]. The high respiratory variations in left ventricular stroke volume help identify an individual patient's "position" on the Frank–Starling curve, with stroke volume variation (SVV) <13% being a very reasonable predictor of fluid non responsiveness [30]. A primary limitation of monitoring SVV and PPV is that larger changes in transpulmonary pressure (i.e., mechanical ventilation) are required for the most reliable results [31, 53]. Small tidal volume mechanical ventilation, spontaneously breathing patients, cardiac arrhythmias, and cases of right or left ventricular failure may yield less reliable results [54, 55]. Additionally, the presence of vasopressors may artificially depress the calculated PPV and SVV, masking hypovolemia [56–58].

Indirect measurement of cardiac output and stroke volume via arterial waveform analysis thus comes closer to an ideal titratable target for fluid management. Systems that provide cardiac output/stroke volume (SV) data via pulse contour analysis require varying degrees of recalibration but may have utility in trending calculated CO/CI [30]. Esophageal Doppler measurement of aortic diameter, blood flow velocity, and calculated cardiac output is another alternative methodology [59]. Transcutaneous transthoracic pulsatile flow assessment due to blood phase shifts calculated from bioreactance data is potentially a more accurate modality than older bioimpedance-based systems [60]. Each of these technologies may provide more dynamic and clinically relevant/trendable data for assessing ongoing VR, with the caveat that titrating to supranormal cardiac performance is not helpful and may even be deleterious [61, 62]. It is an important point to remember that even individuals at euvolemic status may still be volume-responsive. This does not imply that a patient requires volume merely because they have the capacity to increase CO. The decision to administer volume must be made in the context of clinical signs of hypotension or hypoperfusion in addition to the requirement for volume-responsiveness.

While the above parameters allow for 'snapshot' evaluations at one moment in time, it would be ideal to have a continuous parameter that allows the physician to monitor trends over time. Central venous oxygen saturation ($ScVO_2$) is a tempting parameter to do exactly this, however it is an unreliable measure of volume status as it may be clinically elevated due to peripheral shunting [63]. Additionally, there is evidence that higher $ScVO_2$s may even be associated with a higher mortality [64]. Over-resuscitation in patients with septic shock will increase tissue edema and possibly worsen microvascular perfusion; earlier application of vasopressor support to spare increased volumes of administered fluid may need to be considered [65].

A conservative (perhaps a better word is "optimal") fluid management strategy reduces mortality in septic shock [39, 66]. This trend has also been demonstrated with elective surgery [67, 68]and after high-risk surgery by means of rigorous titration of fluid loading to optimization of cardiac output as determined by transesophageal doppler [69, 70]. The association between positive fluid balance during critical illness and mortality is strongest among patients at risk of fluid retention (congestive heart failure and acute kidney injury or chronic renal insufficiency) [33]. Even in the septic shock population, a less positive fluid balance and a restrictive fluid administration approach after the initial resuscitation phase may improve outcomes [4]. This trend does not currently support a "vasopressor heavy" resuscitation strategy, as vasoconstrictor use in the setting of unconnected hypovolemia will likely worsen organ ischemia, and an ongoing balance is required [71].

Excess fluid administration in the face of decreasing VR (assuming you are trending a reliable fluid response metric) will increase extravascular fluid, particularly in cases of capillary leak [33]. The endothelial glycocalyx, a 1-mm thick membrane-bound matrix of glycoproteins and proteoglycans, is compromised in inflammatory states and by hypervolemia [72]. This matrix serves not only as a dynamic intravascular plasma and albumin reservoir but also as a critical vascular barrier function, the disruption of which causes enhanced capillary leak [73].

These data underscore the need to carefully individualize fluid management and to couple it tightly with vasopressor utilization to optimize the hemodynamic picture. This can only be done with a reliable dynamic measure of cardiac output or stroke volume, emphasizing an inherent flaw in EGDT reliance on static measures such as CVP and/or $ScvO_2$. Tracking some measure or surrogate for CO is essential [74, 75].

The choice of which specific resuscitation fluid is best has been a source of extraordinary debate. Colloids, albumin in particular, have been at least an attractive theoretical choice due to the (temporary) sustainment of intravascular oncotic pressure, requirement for smaller volumes, less pulmonary edema, and potentially shorter times to reach therapeutic end points [76]. There has also been the suggestion that albumin may possess antioxidant potential [77]. Albumin may also help stabilize the endothelial glycocalyx [78] . The Saline Versus Albumin Fluid Evaluation (SAFE) trial evaluated albumin versus crystalloid for hypotensive resuscitation and found no mortality differences [79]. Other evaluations of albumin in septic shock have found no mortality advantage, however increased costs/length of stay have been suggested [80, 81]. If albumin is used for volume expansion, slower administration may be more beneficial (3 h), and albumin may be the volume expander of choice in septic patients with cirrhosis [82, 83]. End points for albumin-based volume resuscitation in addition to improved hemodynamic stability have been serum albumin concentrations in the range of 3 mg/dL.

Due to the relatively high alveolar permeability to albumin during septic shock, albumin has not been demonstrated to offer greater lung protection than crystalloids [84, 85]. In the CRISTAL study of all-cause hypovolemic shock, there was a trend with albumin toward more days free of mechanical ventilation, decreased days of vasopressor use, and decreased mortality at 90 days but not at 28 days [86]. Ultimately though, for septic shock, other than crystalloids requiring roughly 1.5–3 times the absolute volume and a slightly longer time to goal resuscitation, albumin has not been shown to be more effective than crystalloids [84, 87].

Hetastarch has likewise not been shown to offer clinical advantages, and its use is associated with potential coagulopathy (Von Willebrand/Factor VIII effects), acute kidney injury, anaphylaxis, and higher mortality in sepsis [88]. Blood substitutes (i.e., polymerized hemoglobin) are also theoretically attractive to enhance oxygen delivery, particularly due to EGDT bundles, which suggest a more aggressive transfusion practice than is supported by the clinical evidence [89]. None of these artificial hemoglobin products have reached significant clinical utilization and are hindered by vasoconstrictive effects (nitric oxide scavenging), acute kidney injury, platelet sequestration, cytokine release, and trends toward higher mortality. Application of these agents may be appropriate when blood is unavailable [90, 91].

Overall, 0.9% sodium chloride (normal saline [NS]) is the most widely used resuscitation fluid [92]. Concern however has arisen that the high chloride content of NS contributes to both acute kidney injury and increased mortality in critically ill patients [93, 94]. The chloride effect on the kidney may be due to afferent renal arterial vasoconstriction [95]. The alternative to NS has traditionally been solutions

such as lactated Ringer's or proprietary "buffered" products—the composition of which more closely resembles plasma. The SMART trial compared 0.9%NS to balanced crystalloids (LR or Plasma-Lyte A) in 15,000 critically ill adults, and found a decreased composite outcome of death, new renal-replacement therapy, or persistent renal dysfunction in patients recieveing balanced crystalloid [96]. In preplanned subgroup analysis, balanced crystalloids were found to have less composite outcome in medical ICU patients, neurological ICU patients, patients with sepsis, patients with TBI, and patients with history of renal replacement therapy. For patients undergoing major abdominal surgery, NS was associated with higher vasopressor requirement than buffered crystalloid [97]. In patients undergoing open abdominal surgery, NS was associated with a higher risk of mortality, surgical site infection, and renal failure compared to balanced crystalloid [98]. NS is also well associated with hyperchloremicnonanion gap metabolic acidosis [99] and may also predispose to a higher incidence of coagulopathy [100].Lactated Ringer's (LR), in addition to having a lower chloride load than NS, serves as a source of myocardial fuel and as a source of glucose [101] . As a base, lactate serves as a source of bicarbonate with a resultant elevation in plasma pH. Despite common misconceptions, the use of LR is not contraindicated in patients with renal impairement, as the amount of potassium present in LR is trivial compared to the extracellular shift of potassium that occurs with administering acidic solutions such as 0.9% NS. Randomized controlled trials of LR vs 0.9% NS in renal transplantation surgeries have shown reduced rates of hyperkalemia and acidosis in patients receiving LR [102, 103]. The use of LR is also not contraindicated in liver disease [104] .Based on these data and the unclear linkage between chloride and acute kidney injury, balanced solutions such as LR and Plasma-Lyte should be favored over 0.9% for the resuscitation of most septic patients.

In summary, the goal of volume resuscitation in a septic patient is to optimize cardiac output and improve tissue perfusion. For most septic patients, this requires early fluid resuscitation (up to or above 30 mL/kg using crystalloids in the initial hours). Notable exceptions to this rule may be patients with clinical hypervolemia such as those with congestive heart failure or end stage renal disease,whose cardiac output may worsen with additional fluid. Fluid resuscitation should consist of an appropriate combination of balanced crystalloids for most patients, and should be combined with albumin after the initial resuscitation. It is necessary and critical to support the patient's blood pressure with vasopressors such as norephinephrine, vasopressin, and/or angiotensin used in conjunction, syngerstically and early on during the resuscitation process. The goal for this early period is to define a target MAP of at least 65 mmHg, or higher in patients with pre-existing hypertension, and use vasopressors as needed to maintain this MAP while completing fluid resuscitation. After this early period of fluid resuscitation, if the patient still requires significant vasporessors or has persistent signs of hypoperfusion, the patient should be evaluated for fluid responsiveness before administering additional fluid. Fluid responsiveness can be assessed in several ways including ultrasound techniques and invasive monitoring techniques. If the patient does not exhibit signs of fluid

responsiveness, additional fluids should be avoided in favor of augmenting pressors and/or inotropes. As the patient's condition has stabilized, one may consider gradual de-resuscitation by allowing the patient to auto-diurese or introducing diuretic therapy as necessary.

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Case Scenario for Fluid Management in Liver Resection

23

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Abstract

Patients undergoing liver resection, especially those with intrinsic liver disease (e.g., alcoholic liver cirrhosis or hepatitis C), frequently demonstrate a prolongation of PT-INR (prothrombin time/international normalized ratio). Simultaneous thromboelastographic tracings, however, typically show a normal coagulation function in these patients, with transient hypercoagulability occurring immediately after the partial hepatectomy. Liver resection reduces the synthetic function of the liver, resulting in a decrease in the level of both procoagulant and anticoagulant factors synthesized by the liver. Concomitantly, there is an up-regulation on non-hepatically synthesized factors, especially factor VIII and von Willebrand factor, which can maintain coagulation. The release of large amounts of factor VIII, von Willebrand factors, and tissue factor from the cut liver parenchyma can activate the coagulation cascade and subsequent fibrinolysis. This can explain the observed decrease in platelet count, fibrinogen (with the formation of fibrin platelet complexes), the increase in D dimer, and the prolongation in PT-INR that is observed when individual coagulation tests are performed. It is therefore not advisable, and dangerous, to base plasma transfusion decisions solely on prolonged PT/INR values.

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Case Scenario

A 59-year-old male is scheduled for open partial right hepatectomy (segments VII and VIII) for resection of colorectal liver metastases. His medical history is significant for rectal carcinoma 2 years prior to his current presentation. He underwent resection of his rectal mass with an ileostomy, which was reversed a few months after its creation. Diagnosis of liver metastases resulted in the initiation of chemotherapy with Folfox (leucovorin calcium, fluorouracil, oxaplatin) and Avastin (bevacizumab) through a right chest port. He now presents for a partial right hepatectomy. His hypertension is controlled on metoprolol and anxiety disorder is treated by alprazolam. He also reports a history of excessive alcohol use for 30 years until 2 years ago (he stopped alcohol use when the diagnosis of rectal carcinoma was made). A transthoracic echocardiography revealed normal biventricular function with no valvular disease. General anesthesia with invasive arterial and central venous monitoring was initiated.

Discussion

Use of Thromboelastography

Patients undergoing liver resection, especially those with intrinsic liver disease (e.g., alcoholic liver cirrhosis or hepatitis C), frequently demonstrate a prolongation of PT-INR (prothrombin time/international normalized ratio). Simultaneous thromboelastographic tracings, however, typically show a normal coagulation function in these patients, with transient hypercoagulability occurring immediately after the partial hepatectomy [1].

While traditional coagulation tests such as PT-INR only measure portions of the coagulation pathway (specifically factors II, V, VII, X, and fibrinogen activity), thromboelastography (TEG) is a bedside blood test that can be used to define the viscoelastic properties of blood [2]. It is able to provide information about platelet activation, clot and fibrin formation, clot stabilization, and lysis, and therefore gives a more comprehensive picture of coagulation status (Fig. 23.1).

Liver resection reduces the synthetic function of the liver, resulting in a decrease in the level of both procoagulant and anticoagulant factors synthesized by the liver. Concomitantly, there is an up-regulation on non-hepatically synthesized factors, especially factor VIII and von Willebrand factor, which can maintain coagulation.

The release of large amounts of factor VIII, von Willebrand factors, and tissue factor from the cut liver parenchyma can activate the coagulation cascade and subsequent fibrinolysis. This can explain the observed decrease in platelet count, fibrinogen (with the formation of fibrin platelet complexes), the increase in D dimer, and the prolongation in PT-INR that is observed when individual coagulation tests are performed.

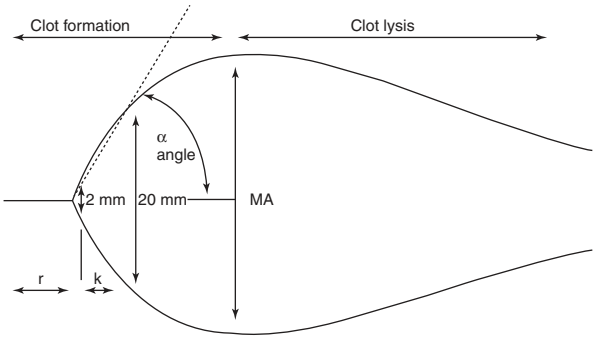

Fig. 23.1 A normal thromboelastographic tracing. (1) *r*—time is the time elapsed from placement of the sample in the cuvette until the tracing amplitude reaches 2 mm; it denotes the rate of initial fibrin formation and is functionally related to plasma clotting factors. (2) *k* is measured from r to the point where the amplitude reaches 20 mm; *k*-time represents the time it takes for a fixed degree of viscoelasticity to be achieved by the forming clot and is affected by the activity of the intrinsic clotting factors, fibrinogen, and platelets. (3) Angle is the angle formed by the slope of TEG tracing from the *r* to the *k* value; it denotes the rate at which the clot is formed. (4) MA (maximum amplitude) is the greatest amplitude on the TEG tracing; it is a reflection of the absolute strength of the fibrin clot and can be altered by both qualitative and quantitative platelet abnormalities

It is therefore not advisable, and dangerous, to base plasma transfusion decisions solely on prolonged PT/INR values. The hypercoagulable state identified in studies following hepatic resection has triggered the use of TEG routinely to guide prophylactic postoperative anticoagulation. In Adult Living Liver donors undergoing right hepatectomy, TEG monitoring showed that more than half of the healthy liver donors rapidly developed a hypercoagulable state following right hepatectomy, despite the use of prophylaxis with low-molecular-weight heparin (LMWH) [3]. Concomitant traditional coagulation tests failed to identify this hypercoagulable state and showed an increased PT-INR, normal activated partial thromboplastin time (aPTT) values, and a reduced platelet count.

In patients with chronic liver disease, all procoagulant factors (with the exception of factor VIII and von Willebrand factor) decrease and levels of anticoagulant factors, antithrombin, and protein C also decline [4]. In response, levels of tissue plasminogen activator and plasminogen activator inhibitors re-equilibrate [5].

The net result of this rebalancing of procoagulant and anticoagulant factors can therefore not be identified by measuring levels of individual factors [6] but requires whole blood coagulation tests (TEG) to provide a true picture of the resultant coagulation status.

Table 23.1 shows the correlation of thromboelastography (TEG) with phases of hemostasis and standard coagulation tests [7].

Table 23.1 Correlation of thromboelastography (TEG))with phases of hemostasis and standard coagulation tests

TEG parameter	Correlation with phases of normal hemostasis	Correlation with standard hemostatic laboratory tests
Reaction time (min)	Time between initiation of coagulation cascade to initial fibrin formation	INR, aPTT, procoagulant factor level
Kinetic time (min)	Time between initial fibrin formation to specific clot firmness	Fibrinogen, platelet count
Alpha angle (degrees)	Rate of fibrin formation and crosslinking	Fibrinogen, platelet count
Maximum amplitude (mm)	Maximum clot strength	Fibrinogen, platelet count
Lysis 30 (%)	Fibrinolysis 30 min after maximum amplitude	Fibrin degradation products

Adapted from [7]
INR international normalized ratio, *aPTT* activated partial thromboplastin time

Choice of Fluids

Balanced crystalloid solutions (Plasma-Lyte, lactated Ringer's solution) are commonly used for initial resuscitation [8, 9]. Crystalloid solutions with a high chloride content (0.9% NaCl) can cause hyperchloremic metabolic acidosis, have been associated with worsening morbidity and mortality [10], and are therefore avoided. Large amounts of hypotonic solution are also undesirable since they can exacerbate extravascular tissue edema.

Hetastarches can contribute to coagulopathy through a dilutional reduction in factor VIII and von Willebrand factor and through a reduction in the accessibility of glycoprotein IIb/IIIa on the surface of platelets [11]. In addition, they worsen renal outcomes and are therefore better avoided [12, 13].

Colloids that do not affect the coagulation profile such as albumin, in addition to correcting volume deficits, can improve splanchnic circulation, reduce bowel edema, and can displace fluid into the intravascular compartment [14, 15]. They are particularly beneficial in patients with low oncotic pressure (e.g., patients with hypoalbuminemia as a result of chronic liver disease) [16, 17].

Intraoperative cell salvage is commonly used in liver resection cases to reduce the need for allogenic red cell transfusion. The decision to transfuse allogenic red cells should take into consideration initial and intraoperative hematocrit, ongoing blood loss, and hemodynamic stability. Management of coagulopathy should be guided by TEG results.

Perioperative blood transfusion has been reported as an independent predictor of outcome (operative mortality, major complications, and hospital length of stay) after liver resection [18, 19]. This effect is dose-dependent with operative mortality between 1 and 2% in patients who received no transfusions, 2.5% in patients who received 1 or 2 units of packed red cells, and 11% in patients who received greater than 2 units of packed red blood cells.

Fluid Management Strategies during Liver Resection

Careful and judicious fluid management is one of the most important strategies to minimize as well as to correct blood loss during hepatic surgery. Fluid therapy during hepatic surgery has to be balanced so as to ensure adequate tissue perfusion and cellular oxygenation while avoiding fluid overload and hepatic congestion, which can lead to difficult dissection and potentially excessive bleeding. A variety of strategies have been utilized during hepatic surgery such as acute normovolemic intraoperative hemodilution, intraoperative cell salvage, restrictive or low central venous pressure (CVP) strategy, as well as liberal fluid replacement strategy.

Fluid restriction by targeting a low CVP has been recommended for liver resections. Low CVP (below 5 mmHg) has been associated with decreased blood loss, requirement for blood transfusions, and length of hospital stay [20–24]. Following hepatic resection, rehydration to a euvolemic state is utilized to ensure adequate perfusion to vital organs. The reported advantages of maintaining a low CVP during liver resection are a result of reduction in the inferior vena cava (IVC) size, which makes it easier for the surgeons to mobilize the liver and the hepatic veins. In addition, hepatic venous distension is reduced and, in case of venous injury, surgical repair becomes more feasible.

However, most of the studies that have supported a low CVP strategy for liver resections were either retrospective or nonrandomized prospective studies that had methodological flaws [20–24]. Moreover, none of these studies showed an improvement in survival or reduction in mortality. This strategy of maintaining a low CVP and a relative hypovolemic state often requires the temporary use of vasopressors to maintain hemodynamic stability especially in the face of IVC manipulation and hepatic vessel clamping. There is also an increased risk of postoperative renal injury. On the other hand, excessive fluid administration results in difficult liver dissection and excessive bleeding as well as subsequent risk of fluid overload [25].

Pulmonary-artery-catheter-based assessment of preload and volume status has been used in patients undergoing liver transplantation without any evidence to support an outcome benefit. Moreover, the use of pulmonary artery catheters has fallen out of favor in the critical care and perioperative setting monitoring [26]. Additionally, pulmonary artery wedge pressure has been shown to be an unreliable indicator of left ventricular filling [27]. Mixed venous or central venous oxygen saturation obtained with a pulmonary artery catheter may provide useful information regarding tissue perfusion and oxygenation in patients with compromised left ventricular failure [28].

More recently, monitoring of dynamic indicators of cardiac preload based on respiratory variations of the arterial pulse pressure have been proposed as having greater reliability in predicting responsiveness to fluid challenge. Pulse pressure variation (PPV) when measured before a fluid challenge can distinguish between responders who are likely to have an increase in their stroke volume with a fluid challenge and nonresponders who are not likely to respond to a fluid challenge [29]. PPV has been shown to be highly sensitive and specific in predicting fluid responsiveness during major hepatic surgery [30].

Surgical Techniques to Limit Blood Loss during Hepatic Surgery

During major liver resections, the inflow of the blood to the liver can be temporarily occluded to minimize blood loss. There are many ways this can be accomplished such as portal triad clamping, total venous exclusion, or selective inflow occlusion where only the inflow vessels supplying a portion of the liver is clamped. Temporary occlusion can be applied intermittently to achieve ischemia preconditioning whereby the clamp is released after a brief occlusion or continuously where the clamp is maintained for an extended period of time.

Portal triad clamping, also known as the Pringle's maneuver, is often used to minimize blood loss during major hepatic resections. A normal liver tolerates up to 60 min of warm ischemia whereas a diseased, cirrhotic liver may only tolerate up to 30 min of ischemia. Longer periods of occlusion typically result in more significant ischemia reperfusion injury to the liver, which is likely to increase morbidity. Intermittent clamping allows for ischemia preconditioning and can help minimize liver injury [31]. Intermittent clamping also allows for longer duration (>75 min) of liver ischemia [32]. Portal triad clamping has been associated with reduced blood loss, by about 800 ml, reduced postoperative liver damage but no resultant impact on liver failure or mortality [33].

Portal triad clamping results in a 40% increase in the systemic vascular resistance and a 10% reduction in the cardiac output. The net effect is an increase of about 15% in the mean arterial blood pressure [34]. This is a result of increased afferent discharge from the sympathetic fibers in the hepatic pedicle. This effect can be blocked by infiltration of the hepatic pedicle with local anesthetics prior to clamping [35].

Total vascular exclusion (TVE) is accomplished by clamping the inflow in the porta hepatis as well as clamping of the infra- and the supra-hepatic vena cava. This allows for a near bloodless field during parenchymal transection. The liver can tolerate up to 60 min of warm ischemia with total vascular exclusion. TVE involves greater mobilization of the liver and the inferior vena cava to allow for placement of the supra- and infra-hepatic clamps. Once TVE has been instituted and hepatic resection initiated, hepatic resection has to be completed prior to unclamping.

Since the inferior vena caval blood flow is temporarily interrupted, there is a significant drop in the preload (up to 80%) with TVE, which often requires volume loading and temporary need for vasopressors. TVE results in a marked drop in cardiac output (up to 40%) and mean arterial pressure (up to 10%) and an increase in heart rate and systemic vascular resistance [36]. Intravascular volume status, presence of portosystemic shunts, and cardiovascular function (ventricular function) affect the response to the caval clamps and whether a patient will tolerate TVE.

In a recent Cochrane review, TVE was not found to be associated with a decrease in blood transfusion requirements [37]. Intermittent portal triad clamping was found to be better than continuous portal triad clamping in patients with chronic liver

disease. This benefit of intermittent clamping was not seen in non-cirrhotics. Also, there was no benefit in instituting selective inflow occlusion as compared to portal triad clamping. Therefore, TVE is best restricted for resection of tumors that have hepatocaval extension or as a last resort if other techniques have failed [38, 39].

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Case Scenario for Fluid Management during Major Spine Surgery

24

Verna L. Baughman

Abstract

Lumbar spine surgery is becoming a common surgical procedure in the geriatric population. It is associated with the potential for acute and massive blood loss, hypotension, anemia, cardiac ischemia, and increased perioperative complications. Fluid status evaluation and management are the central foci for detecting and treating hypovolemia. This chapter on case management focuses on the perioperative management of a typical 72-year-old man, with cardiac and pulmonary disease, coming for a T7 to pelvis laminectomy with instrumentation. This is his third such procedure. The chapter includes discussion of the importance of intravascular volume assessment and management. It describes fluid monitoring techniques, blood conservation therapies, and the prone surgery risks. The patient is presented in reference to current literature describing the anesthetic management and concerns.

Key Points

1. Major spine operations should be classified as high risk due to the length of the surgery, large blood loss requiring significant volume replacement, need for blood transfusion, and risk of organ ischemia/injury if intravascular volume is not maintained.
2. The prone position alters normal intravascular volume distribution, causing peripheral pooling, increased vena cava pressure, and decreased preload leading to a reduction in cardiac output and hypotension.

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3. New monitoring modalities, such as pulse pressure wave form variation with respiration, may help anesthesiologists determine whether cardiac preload is adequate to maintain cardiac output and organ perfusion.
4. Increasing the vasopressor dose needed to support blood pressure may indicate inadequate intravascular volume.
5. Although there are many techniques to decrease intraoperative blood transfusions, most are not useful or have limited effectiveness for major spine surgery in the elderly population.

Introduction

As the population ages, the number of surgeries for the geriatric patients increases, based both on an increase in the number of people in this age bracket and an increased incidence of surgery on this older and more frail population. Specifically, between 2001 and 2010 the number of spine fusion surgeries increased from 46 to 80 per 10,000 and the estimated charges increased from $13.3 billion to $49.9 billion [1]. It is only expected that this trend will continue, with older patients having more chronic medical conditions scheduled for large spine surgery.

Medical optimization of the spine surgery patient is essential to make surgery safe. The goal of perioperative physicians is to optimize the patient's preoperative condition, enhance intraoperative care, and improve postoperative outcome. Perioperative risk stratification is based on overall health as well as specific organ function (heart, lung, liver, kidney, brain, and spinal cord). Current discussions about "prehabilitation" appear in orthopedic and anesthetic patient assessment literature, with the goal of improving nutritional status and exercise endurance in addition to optimization of organ function [2]. Since much spine surgery is elective, this enhanced patient preparation appears reasonable. The aim is to improve postoperative outcome, decrease patient morbidity and mortality, and address perioperative concerns such as fluid balance, anemia, pain control, stress response, and cognitive dysfunction.

Spine surgery can be elective (spinal stenosis, herniated disc) or urgent (metastatic disease, acute cord compression, or fracture causing progressive neurologic deficits). Anesthesia technique depends on the surgical needs, neurophysiologic monitoring, and the patient's associated medical conditions. Complex spine fusion surgery with instrumentation is quite different from surgery for a single-level disc herniation, which is frequently performed on an outpatient basis. Current spine procedures are more invasive, longer, and accompanied by significant blood loss and intravascular volume fluid shifts.

Spine fusion surgery presents the anesthesiologist with the complex problem of maintaining intravascular volume with appropriate fluid management. This concern is related to the potential for significant and acute blood loss and altered cardiac and respiratory physiology. The following physiologic changes and their consequences are modulated by aggressive intraoperative fluid management (Table 24.1).

Table 24.1 Physiologic changes of intravascular volume and fluid management

Physiology	Effect	Result
Anemia	Decreased oxygen delivery	Neuro/cardiac ischemia
Hypotension	Decreased organ perfusion	Neuro/cardiac ischemia
Hypertension	Hyperdynamic state	Increased bleeding and myocardial oxygen consumption
Transfusion	Inflammatory reaction	TRALI, transfusion reactions
High PEEP	Decreased venous return	Decreased cardiac output, increased systemic vascular resistance
Large lung tidal volume	Decreased venous return	Lung injury, decreased preload
Prone surgery	Decreased venous return, interstitial edema, pressure/tissue ischemia	Epidural vein engorgement, facial/airway edema, POVL, neuromuscular injury

TRALI transfusion-related acute lung injury, *PEEP* positive end expiratory pressure, *POVL* perioperative visual loss

This chapter will discuss an older patient with acute/chronic back pain scheduled for an extensive reoperative spine surgery. Much postoperative morbidity and mortality relates to intraoperative fluid management; therefore, the focus of this case study is on fluid management. The *shaded* sections discuss the management of this patient.

Case History: The Typical Patient

The case is about a patient scheduled for reoperativethoraco-lumbar spine surgery. This 72-year-old gentleman is to undergo T7 to L5 laminectomy with removal of existing hardware and instrumentation from T5 to S1. This is his third spine operation, with a previous L1–L3 stabilization and later with an extension from T10 to L5. He presents with severe back pain, with radicular pain radiating to both hips and legs. His computed tomography (CT) and magnetic resonance imaging (MRI) scans show spondylolisthesis, recurrent disc herniation, spinal stenosis, and nonunion of some of the previous fusion levels. His medical history is significant for coronary artery disease (CAD), hypertension, non-insulin-dependent diabetes mellitus, obesity, current alcohol use, and mild to moderate chronic obstructive pulmonary disease (COPD). He has a 50 pack year smoking history and still continues to smoke, although his surgeon strongly advised him to stop since smoking decreases bone regeneration and can inhibit postoperative bone fusion. The electrocardiogram (ECG) showed T-wave changes in the inferior leads and the chest X-ray (CXR) was consistent with COPD (Table 24.2).

His cardiac history is significant for non-ST-segment elevation myocardial infarction (NSTEMI) 10 years ago, treated with two drug-eluting stents (DES). Current echocardiogram shows mildly dilated, hypertrophic cardiomyopathy with asynchronous wall motion in the septal and inferior walls. He is followed by a cardiologist who says that his transthoracic echo has been stable over the past few

Table 24.2 Patient profile

Patient profile	
Age	72 years
Gender	Male
Height	68 in
Weight	120 kg
Obesity	BMI 42
Cardiac	MI 10 years ago
	Two drug-eluting stents 10 years ago
	Stable ejection fraction 35–40%
	Stable echocardiogram
	Aspirin and clopidogrel stopped 6 days ago
Hypertension	Lisinopril/HCTZ 20/25 mg qAM
	Metoprolol 50 mg BID
COPD	Mild
Diabetes	Type II
	Hgb A1c 8.5%
	Metformin 1000 mg/day
Renal	BUN/Cr 45/1.4
Liver	Normal LFTs
Mental status	Age appropriate
Social history	Tobacco: 1 ppd. × 50 years
	Alcohol: 2 drinks per day
Vitals	BP 145–165/70–80, HR 78, sat 95%

BMI body mass index, *MI* myocardial infarction, *HCTZ* hydrochlorothiazide, *Hgb* hemoglobin, *BUN* blood urea nitrogen, *Cr* creatinine, *LFTs* liver function tests, *ppd* packs per day

years with an ejection fraction of 35–40% and normal valve function. However, the most recent study is incomplete because target heart rate was not obtained. He is taking clopidigrel and aspirin. His hypertension is treated with an angiotensin-converting enzyme (ACE) inhibitor, hydrochlorothiazide, and a beta blocker. His non-insulin diabetes is reasonably well controlled on metformin with an HgA1c of 8.5 and daily glucose levels of 130–150 g/dl. His cardiac risk, as determined by both his cardiologist and internist, is moderate for moderate-risk surgery.

However, this surgery (which was once considered moderate-risk surgery) should now be classified as high-risk surgery with the expectation of significant blood loss and fluid shifts. This change in spine fusion surgery classification is recognized by many anesthesiologists, but has not yet filtered into the medical/surgical risk literature [3, 4].

Discussion

Hypertension, Hypotension, and Spine Surgery

Poorly controlled hypertensive patients pose a serious question: What is the patient's baseline blood pressure? This information may be obtained from the patient's

medical records from his internist, orthopedic surgeon, anesthesia preoperative clinic, or on the day of surgery. Which is correct? Frequently, a patient claims that his blood pressure is elevated because he is in pain, forgot to take his medication that day, is noncompliant, or actually is poorly controlled. This is important because the anesthesiologist needs to define a baseline pressure so that intraoperative limits can be established.

Surgeons often request intraoperative hypotension to decrease blood loss and improve operating conditions. Since much blood loss during spine surgery is from distended epidural veins and not from arterial bleeding, extremely low systolic blood pressure management may incur risks without providing significant benefit. Poorly controlled hypertensive patients have more hemodynamic instability, and the optimal blood pressure range to prevent organ ischemia has not been defined. Therefore, most anesthesiologists review historical records, determine the average baseline blood pressure over time, and use this as the target intraoperative pressure goal.

The concern about hypotension is further supported by recent studies that show intraoperative hypotension is associated with 30-day postoperative mortality: mean arterial pressure [MAP] decrease of more than 50% from baseline for more than 5 min [5]; intraoperative hypotension with MAP < 60 mmHg for more than 11 min promotes acute renal injury [6]; and a low blood pressure associated with low minimum alveolar concentration (MAC) and low bispectral index system (BIS) is associated with postoperative mortality [7].

Fluid Management

Changes in intravascular volume affect blood pressure, cardiac output, and coronary perfusion. Acute blood loss, which occurs during surgical resection, can adversely affect homeostasis. For a detailed description of the methodologies used to monitor intravascular volume see Chap. 5.

Historically, intravascular volume was determined by urine output. If less than 0.25–0.5 ml/kg/h, the anesthesiologist administered intravenous (IV) fluids until urine output increased. This frequently resulted in an edematous patient with significant volume overload and occasionally evidence of congestive heart failure. Monitoring adequacy of intravascular volume advanced with the use of a central venous pressure (CVP) catheter in an attempt to improve volume management. Monitoring CVP) transitioned to the use of the pulmonary artery catheter to measure pulmonary vascular and wedge pressures. Intermittent cardiac output (CO) values measured with 10 ml of ice water injections transitioned to continuous cardiac output evaluations. Now the transesophageal echo (TEE) provides anesthesiologists with a visual evaluation of ventricular chamber size and wall motion, changing the evaluation from pressure measurements to volume measurements. These invasive technologies have increased the clinician's ability to determine whether a patient needs additional intravascular volume, has been adequately volume resuscitated, or is volume overloaded.

Table 24.3 Changes with prone position

Cardiac	Decreased cardiac index
	Decreased preload
	Increased SVR
	Increased PVR
	IVC compression/obstruction
Respiratory	Decreased lung volumes
	Altered pulmonary blood flow
Nervous system	Vascular occlusion
	Cervical spine injury
	Peripheral nerve injury
Pressure injury	Direct tissue pressure
	Contact dermatitis
	Periorbital edema
	Facial swelling
Indirect pressure	Macroglossia
	Oropharyngeal edema
Embolic complications	Air 2–5%, thrombus 2%
Visceral ischemia	
Mediastinal compression	
Limb compartment syndrome	
Rhabdomyolysis	
Vision loss	

SVR systemic vascular resistance, *PVR* pulmonary vascular resistance, *IVC* inferior vena cava

New approaches to determining volume status involve intra-arterial and noninvasive finger cuff pressure wave form evaluations. They analyze the variation in wave form amplitude during positive pressure ventilation (PPV). A decrease in amplitude during the inspiratory phase of positive pressure ventilation suggests the patient needs additional volume to increase venous return and enhance cardiac output. The esophageal Doppler is another new monitor that is being tested to predict whether the patient is "fluid responsive" by measuring the respiratory variation of aortic blood flow and whether a IV fluid bolus improves the patient's cardiovascular status. Multiple studies are evaluating the validity of these technologies; however, none involve the prone position. Normal pressure values change from supine to prone positioning, without a change in total intravascular volume, so how reliable are these monitors? (Table 24.3).

Monitoring the Patient in the Prone Position

The prone position increases intrathoracic and intra-abdominal pressures, depending on the prone support system used. Measurement of systemic blood pressure can be problematic with both a routine noninvasive blood pressure cuff (surgical team

leaning on the cuff and/or kinking of the pressure tubing) and with an intra-arterial line (with arms tucked and catheter obstruction) . These blood pressure measurement problems are not bypassed by the newer technologies, which require a stable arterial pressure tracing or accurate cuff pulsatile pressure recordings. Clinicians are still faced with the "art of volume management," assisted by additional monitors that may, or may not, provide important information. It requires accurate evaluation by the anesthesiologist to determine whether the data provided by these new technologies are valid or erroneous.

Monitoring intravascular volume technology:

- Urine output
- CVP
- Pulmonary artery catheter pressures or wedge pressure
- Arterial line (systolic, mean, diastolic)
- PPV (pulse pressure variation with arterial or pulse oximetry wave tracings)
- PPI (peripheral perfusion index with noninvasive finger cuff)
- Pulmonary elimination of CO_2
- SVV (stroke volume variation using arterial pressure wave to calculate cardiac output)
- CNAP (continuous noninvasive arterial pressure)
- Pulse oximetryphotoplethysmography
- Esophageal Doppler
- TEE (transesophageal echo)

Interaction between surgeon and anesthesiologist is critical. Anticipation of surgical blood loss permits the anesthesiologist to preemptively adjust intravascular volume with crystalloid or colloid infusions to compensate for the projected blood loss. Lack of communication puts the patient at risk and the anesthesiologist in a "catch up" situation. Decreased preload leads to decreased stroke volume, tachycardia, low blood pressure, decreased diastolic myocardial perfusion, and brain/spinal cord/cardiac/renal ischemia. The anesthesiologist's intuition, supported by knowledge of the surgical procedure, and awareness of the surgeon's technique assist in planning the volume management of the prone surgical spine patient.

Blood Conservation

Blood loss and the need for multiple blood product transfusions is a serious concern for extensive spine fusion surgery. The transfusion rate for this surgery has been quoted to range from 50 to 81% [8]. Bleeding is both arterial and venous. Arterial bleeding may be decreased by reducing blood pressure. Venous bleeding comes from distended epidural veins and raw bony surfaces after removal of the cortical bone. Blood loss for the same operation by the same surgeon can range from 300 to 3000 ml [9]. Lumbar spine fusion involving instrumentation increases blood loss by approximately 50% and reoperation increases it by another 20% [10, 11].

Transfusion philosophy:

- Patient is actively and rapidly losing blood
- Blood loss is expected to continue
- Patient is currently anemic
- Patient has significant cardiac/pulmonary disease
- Patient is requiring increasing vasopressor dose to maintain blood pressure
- Patient is requiring increasing vasopressor dose despite hypotension
- Transfuse after the major blood loss has occurred in order to decrease the amount of blood needed

Because this extensive surgical procedure has the potential for significant blood loss, continual determination of adequate intravascular volume is essential, including anticipation of blood loss, preemptively treating with crystalloid/colloid, and administration of blood products to prevent hypovolemia, hypotension, and anemia.

In 2012, Mathai described and validated a statistical model that could account for 75% of the variability of blood loss [12]. It contains only four items: the number of laminectomy levels, whether bone was harvested from the iliac crest, experience of the surgeon doing the initial exposure and closure, and distension of the epidural veins. The Jackson table, which avoids abdominal compression and decreases distension of the epidural veins, was used for all of these operations. Blood loss averaged 1167 ± 998 ml with a range from 32 to 3745 ml [12]. Use of other support systems will increase anticipated bleeding. The type of fusion may also affect blood loss because interbody fusions require more exposure.

Factors that predict blood loss:

- Patient age
- Preoperative anemia
- Multiple osteotomies/fusions
- Preexisting cardiac/pulmonary disease
- Spine tumor surgery
- Number of spinal levels fused
- Type of surgical support frame (Jackson table recommended)
- Wilson frame increases blood loss
- Surgical technique
- Long surgical time
- Elevated arterial pressure
- Elevated venous pressure (distended epidural veins)
- Type of anesthesia (spinal/epidural decrease blood pressure and blood loss)
- Dilutional coagulopathy
- Primary fibrinolysis

Blood Conservation Therapies

Multiple blood conservation therapies have been proposed to decrease intraoperative blood loss and the risk of transfusion-related injuries. These include enhanced hematopoiesis, hypotension, antifibrinolytics, recombinant factor VII, preoperative autologous donation, acute normovolemichemodilution, cell saver technologies, desmopressin, and prothrombin complex concentrates [13].

Enhanced Hematopoesis

Chronic inflammatory conditions impair the body's ability to mobilize iron from storage sites and limit hematopoesis. Preoperative oral iron is frequently poorly tolerated and has poor gastrointestinal (GI) absorption in addition to causing constipation. Intravenous iron supplementation and intramuscular (IM) erythropoietin treatments are costly and require hospital/clinic visits for administration. The use of preoperative erythropoietin only appears to decrease transfusion requirements for small spine surgery, not extensive surgery [14]. "Prehabilitation" with adequate nutrition may help ameliorate this problem, but it needs to be started at least several weeks prior to scheduled surgery.

Hypotension is currently being used less because of a concern for inadequate tissue perfusion and organ ischemia. Hypotension does decrease arterial blood loss and improve surgical field visibility but is associated with cardiac, neurologic, and renal injuries.

Antifibrinolytic agents inhibit fibrinolysis and prevent clot breakdown. A meta-analysis reviewed the efficacy of aprotinin, transexamic acid, and epsilon aminocaproic acid in reducing blood loss and transfusions during major spine surgery. This review of 18 trials demonstrated equal efficacy of all three drugs [15]. However, in 2007 the US Food and Drug Administration (FDA) removed aprotinin from the market because of an increased risk of long-term mortality in cardiac surgical patients.

Recombinant factor VII concentrate is used to manage hemophilia-related bleeding. It enhances the natural coagulation pathway via the formation of tissue factor–factor VIIa complexes at the site of endothelial damage. It has an increased risk of arterial thrombosis (stroke, death) and may not confer additional benefit over other treatments for spine surgery.

Preoperative autologous donation can decrease the risk of homologous transfusions by up to 50%. A healthy patient can donate 2–4 units in the 8 weeks prior to surgery and still have a near normal hematocrit the day of surgery, but this requires time and planning. If a patient donates only several days prior to surgery he or she may be anemic and require more/earlier transfusion than if they had not donated. Since these units are stored in the blood bank, the potential for administering the

wrong unit still exists. At least 1 unit of predonated blood is wasted in 50% of scoliosis patients. These wasted autologous units cannot be used for other patients because of incomplete initial screening. Additionally, people who weigh less than 50 kg are not candidates for this process.

Acute normovolemichemodilution removes several units of blood while simultaneously replacing this volume with crystalloid or colloid so that the patient remains normovolemic. It requires an arterial line and several large-bore intravenous catheters. It should only be used for patients without cardiac/pulmonary pathology and who are expected to lose a large amount of blood. Since tissue perfusion does not decrease with a hematocrit of 22–25%, provided there is adequate intravascular volume and cardiac output, this technique is safe. In fact, oxygen delivery may increase because decreasing the hematocrit improves rheology and tissue microperfusion. This is a labor-intensive process and in a recent meta-analysis this blood conservation measure demonstrated a likely reduction of only 1 unit of red blood cells, questioning its usefulness [16]. Isovolemichemodilution does not affect the volume of blood lost, but it decreases the amount of red blood cells lost. After the majority of surgical blood loss has occurred, the patient is transfused with his own blood, which contains red cells, platelets, and clotting factors. Frequently, a diuretic is needed to rid the patient of the excess volume that was administered to keep intravascular volume normal during the surgery.

Cell saver salvage techniques are very useful in cardiac surgery because a larger suction catheter is used (less cell lysis) and the blood salvaged from the pericardium is relatively free of other substances (bone fragments, fat). Therefore, the cardiac surgery salvage return of 60–70% is reduced to 30–40% for spine surgery. Using this technology, the number of transfused units to a patient with an estimated blood loss of 4000 cc would decrease transfusion requirements from 6 to 4–5 units of packed red blood cells (PRBCs). The average hematocrit of this salvaged blood is around 40%. Another reason for the decreased recovery rate is the liberal use of sponges by spine surgeons.

Desmopressin (DDAVP) stimulates release of factor VIII and von Willebrand factor from the endothelium, which enhances platelet aggregation. Its effectiveness for bleeding surgical patients has not been consistently shown.

Prothrombin Complex Concentrate (*PCC*) is recommended for urgent reversal of vitamin K antagonists and to treat hemophilia B. They contain either three or four anticoagulant factors (II, IX, X, and sometimes VII). PCC has recently been shown to effectively reverse dabigatran-induced anticoagulation in pigs [17] at 50 u/kg. Higher doses were associated with a potential for hypercoagulation. Because fibrinogen decreases with bleeding it may be necessary to administer fibrinogen. PCC requires no crossmatch and can be given rapidly with minimal risk of volume overload. It has a small risk of infection.

New technology, including the use of hemostatic/sealant agents during surgery, new methods of surgical cautery, and changes in surgical technique (i.e., minimally invasive robotic surgery) may limit blood loss.

Intraoperative Hypotension, Anemia, and Cardiac Ischemia

Cardiac ischemia occurs in patients with diffuse coronary artery disease. Myocardial ischemia is caused by an imbalance between supply and demand. The two major mechanisms are: (1) acute coronary occlusion by plaque/thrombus and (2) decrease in oxygen supply by hypotension/anemia and/or an increase in myocardial oxygen consumption. The first category might be produced by surgery-induced hypercoaguable state, the administration of antifibrinolytic agents, or the rebound effects of stopping clopidogril/aspirin. The second category can occur during extensive spine surgery in association with significant blood loss producing anemia, hypovolemia, and hypotension.

Case Scenario (Continued)

Both of these mechanisms of coronary ischemia are of real concern for our patient. For these reasons, adequate intravascular volume was maintained (except for one episode of acute blood loss and hypotension). Antifibrinolytic drugs were not used because of his cardiac history and the concern for stent thrombosis.

Elective hypotension during spine surgery has almost disappeared because of these problems. It is thought that the reason the POISE trial (use of beta blocker metoprolol to decrease intraoperative cardiac ischemia) showed a higher incidence of stroke was because of hypotension. Hypovolemia, hypotension, and anemia can produce tachycardia, which may be blocked in many patients who are on chronic beta blockade therapy, thereby masking a warning sign of hypovolemia.

Case Scenario (Continued)

Even though our patient was on a beta blocker, he became tachycardic with acute hemorrhage. However, this reflex tachycardia did not improve his blood pressure or cardiac output and may have been the etiology of his elevated postoperative troponin levels.

The risk of postoperative cognitive decline (learning and memory impairment) may also be linked to intraoperative anemia causing neuronal hypoxia. A recent review of data from The American College of Surgeons' National Surgical Quality Improvement Database evaluated outcomes of 227,425 noncardiac surgical patients with regard to preoperative anemia. Anemia was defined as mild (hematocrit [Hct] between 29 and 39%) or moderate to severe (Hct < 29%). This evaluation demonstrated that even mild anemia was associated with an increased risk of 30-day morbidity and mortality [18].

Case Scenario (Continued)

Our patient does not have preoperative anemia, but does have multiple cardiac risk factors and is to undergo extensive spine surgery associated with large blood loss. His elevated preoperative hematocrit is due to his smoking history, which reflects potential organ damage with a small decrease in hemoglobin concentration. Therefore, many of the blood conservation methods may not be appropriate.

Because of our patient's age, associated medical problems, and extent of the surgery (multiple levels, reoperation, removal of previous instrumentation, and implantation of new instrumentation), he had an arterial line inserted prior to induction of anesthesia. Both arms were placed on arm boards and available to the anesthesiologist for adjustment of the arterial catheter when the fidelity of the wave tracing was questionable. Pulse pressure variation (PPV) measurements were recorded from the arterial line and used as a basis of intravascular volume determinations (Table 24.4).

With acute massive blood loss, PPV changed from 14 to 30, indicating a significant decrease in preload and stroke volume. Crystalloid (6 l), colloid (albumin 1500 ml), and blood products (4 units PRBC, 3 units fresh frozen plasma [FFP], and 2 units pooled platelets) were administered with the return of PPV to 10. Blood gas changes reflect intravascular volume status (Table 24.5).

The Surgery

The goal of surgery is to stabilize the affected segments and to decompress neural elements. Spondylolisthesis, a forward slippage of one vertebral body in relation to the body below, may involve motor, sensory, and reflex changes. It presents with back pain, radiculopathy, neurogenic claudication, and facet/ligament hypertrophy. Disc herniation may be present. Flexion, by sitting or leaning forward, increases

Table 24.4 Hemodynamic changes—supine, prone, acute blood loss, and volume replacement

Position	Blood pressure (mmHg)	Heart rate (bpm)	CVP (cmH_2O)	Cardiac output (CO L/min)	Pulse pressure variation (PPV)	BIS (Bispectral Index)
Awake, supine	140/70	54	–	–	–	97
Anesthesia:						
Supine	132/65	50	12	4.2	10	48
Prone	106/50	62	18	3.3	14	52
Acute blood loss	70/45	109	8	1.4	30	23
After volume replacement[a]	110/70	58	14	3.8	11	51

[a]Six liters crystalloid, 4 units packed red blood cells (PRBCs), 3 fresh frozen plasma (FFP), 1500 ml albumin, 2 units platelets

Table 24.5 Blood gas changes with acute hemorrhage

	Baseline—prior to induction	Acute blood loss—hypovolemia	Volume resuscitation (PRBC, FFP, albumin, platelets)[a]
pH	7.45	7.09	7.40
PCO_2	45	28	35
PO_2	89	58	78
HCO_3	31	20	26
Hgb/Hct	15/45	7/21	13/39

[a]Six liters crystalloid, 4 units packed red blood cells (PRBC), 3 fresh frozen plasma (FFP), 1500 cc albumin, 2 unit platelets; Hgb/Hct – hemoglobin/hematocrit

spinal canal size by stretching the protruding ligamentumflavum, reduction of overriding facets, and enlargement of the foramina.

Case Scenario (Continued)

Our patient has significant and recurrent spinal cord and nerve injury, producing severe pain that limits his daily activities and requires significant narcotic analgesia. His recurrent central spinal stenosis and spondylolisthesis were evident on MRI and CT scans.

Imaging is used preoperatively to localize the site and extent of disease and intraoperatively to assist in the placement of pedicle screws and intervertebral disc implants, which can injure nerve roots and spinal cord. Hardware can fail or migrate, which happened to this patient. The proposed surgery required multilevel segmental instrumentation and fusion to maintain the new alignment. Fusion is obtained by using pedicle screws and rods. Morcelized bone may be placed between vertebral bodies to reinforce the screw/rod complex fusion. The surgery involves extensive dissection around muscles, periostium, and bone in addition to extensive decortication of spinal bone elements. Exposure of cancellous bone and bone marrow activates the coagulation cascade and the fibrinolytic system. Injury to soft tissue (skin, muscle), bone, and periostium produce intraoperative bleeding and postoperative tissue swelling and edema. Depending on the extent of surgery, operative time can range from 100 min to more than 12 h and IV fluid administration from 1.5 to 20 l.

Indications for laminectomy, fusion, and instrumentation:

- Neurologic signs (myelopathy, radiculopathy, neurogenic claudication)
- High-grade spondylolisthesis >50%
- Unstable spine
- Acute onset of severe neurologic deficit (e.g., paralysis, bowel/bladder incontinence)
- Traumatic spondylolisthesis
- Iatrogenic spondylolisthesis

- Spine mass (tumor, cyst, infection)
- Postural deformity
- Incapacitating pain after conservative treatment

Vascular Injury

Venous laceration is the most common vascular injury. Arteries are more elastic and movable than veins and therefore less likely to be injured during dissection and retraction. Arterial injury is often caused by deep rongeur bites beyond the anterior spinal ligament [19]. This can produce large intraoperative blood loss, which is associated with hemodynamic instability, and increased mortality rates to 15–65% [20]. Although massive arterial blood loss is evident, the continuous venous oozing can produce a significant and progressive decrease in intravascular volume unless the anesthesiologist compensates with crystalloid/colloid/blood administration.

Fluid Management and Postoperative Vision Loss

Postoperative vision loss (POVL) is closely related to intravascular volume. The incidence is between 1/60,000 and 1/125,000. Spine surgery accounts for up to 70% of visual loss cases. It occurs when the optic nerve becomes ischemic, possibly due to decreased blood flow in the retinal artery caused by edematous interstitial tissue compressing the fragile perforating arteries that feed the optic nerve or from increased venous pressure [21]. Several retrospective evaluations have proposed that precipitating factors include obesity, male gender, long surgical times, prone position, large blood loss, significant crystalloid administration in relation to colloid, and use of the Wilson frame for surgical positioning [22]. Anemia and hypotension may also contribute to this serious condition; therefore, it is reasonable to maintain adequate blood pressure, intravascular volume, and oxygen carrying capacity. POVL is frequently not diagnosed immediately after surgery because the patient may be too sedated to evaluate. This condition does not respond to treatment and is usually bilateral and permanent.

Case Scenario (Continued)

Because our patient is to undergo a long surgical procedure with fluid shifts producing tissue edema, the American Society of Anesthesiologists (ASA) recommends that this potential complication of blindness be part of the preoperative discussion [23]. Patients prefer this to be by the surgeon in his clinic, and not on the day of surgery.

Prone Positioning

The prone position puts the patient at risk for many reasons. It decreases venous return and reduces cardiac output and blood pressure. Treating this hypotension with excessive volume administration can cause problems. Judicious administration of fluids and use of vasopressors can improve perioperative outcome.

Positioning options:

- Regular operating table with blanket/gel rolls supporting pelvis and shoulders
- Wilson frame
- Jackson table
- Kneeling position
- Knee-chest position

Abdominal compression of the inferior vena cava shifts venous return from lower extremities to the azygous system, a valveless epidural venous plexus. This bypass route around the compressed vena cava produces engorged epidural veins, which bleed easily and are difficult to control surgically. It obscures the surgical field while dissecting connective tissue, bone, and disc material from nerve roots and the spinal cord. Correct prone positioning decreases or eliminates this upward pressure on the abdomen. If the abdomen hangs free, venous blood flows away from the spinal epidural veins and into the vena cava. Operating tables that do not compress the abdomen (i.e., Jackson table) produces less blood loss while facilitating ventilation. Prone positioning can cause patient injury and constant attention is needed [24].

Requirements for the prone position:

- Firm bolsters at chest and iliac crest level
- Arms tucked or abducted <90° to decrease brachial plexus injury
- Abdomen free from compression to improve venous return
- Decreased epidural vein volume/pressure
- Reduce lower extremity venous stasis/thrombosis
- Protect eyes
- Neck in neutral position

Intraoperative Neurophysiologic Monitoring

The use of neurophysiologic monitoring of somatosensory evoked potentials (SSEP) and transcranial motor evoked potentials (TcMEP) has become routine. The goal is to provide a warning system to prevent spinal cord and nerve injury from surgical manipulation. If SSEP amplitude decreases 50% and latency increases 10%, or if TcMEP tracings disappear, there is concern for neuronal injury. Since hypovolemia and anemia can produce spinal cord ischemia, intravascular volume status must be

evaluated whenever there is a change is these monitors to distinguish surgical trespass from volume status.

Spinal Surgery Complications

Complications of surgery include major blood loss, infection, postoperative respiratory compromise, cardiovascular injury, frequent blood transfusions, spinal cord and nerve root injury, air embolism via open epidural veins, and paralysis [25]. In a review of 5887 patients from NSQIP (2005–2010), Schoenfeld found that 0.4% died after surgery and 10% sustained a complication. Risk factors associated with mortality included age more than 80 years, pulmonary compromise, large body mass index (BMI), ASA class greater than II, preexisting neurologic injury, increased surgical time, and albumin less than 3.5 g/dl [26].

Case Scenario (Continued)

Using these criteria our patient has many of these risk factors and is at great risk for acute blood loss and intraopertivehypovolemia producing significant hypotension.

Similarly, Carabini developed a surgical complexity score that includes preoperative anemia, surgical complexity, anticipated duration of surgery, and number of levels instrumented. Approximately 60% of major spine fusion patients receive a transfusion that is also associated with increased postoperatipve morbidity (cardiac = 9%, thromboembolic = 9.5%, and infection = 8.5%) [4]. Therefore, preoperative evaluation and risk assessment need to be revised for major spine fusion surgical patients.

Anesthesia Concerns

Anesthesia

Anesthesia technique is specific to neurophysiologic monitoring needs. SSEP tracings can be altered by hypothermia, hypocapnia, hypoxia, hypotension, and anemia. These conditions can all be produced by hypovolemia associated with acute blood loss. The use of muscle relaxants can improve the SSEP signal by decreasing baseline signal interference; however, this may not be employed if motor-evoked potentials are also monitored. If TcMEP monitoring is used, or if baseline spinal cord injury is severe, TIVA (propofol and a narcotic) is the anesthesia of choice because it suppresses the signals the least. Inhalational anesthesia has more of an effect on TcMEP because there are more synapses and the anesthesia gases produce a decrement of signal at each synapses.

Case Scenario (Continued)

For our patient, TIVA anesthesia was used to permit accurate evoked potential monitoring. A processed electroencephalogram (EEG) monitor was used to measure depth of anesthesia. Nitrous oxide was not used because of the concern for air embolism and its depressant effect on evoked potential monitoring. Muscle relaxation was used for intubation but was reversed for spinal cord monitoring.

Use of vasopressors is important in maintaining blood pressure during surgery. Anesthesia agents produce veno-vaso dilation and decrease cardiac contractility, which leads to a decrease in blood pressure and spinal cord perfusion. The two most commonly used vasopressors are phenylephrine and norepinephrine. Phenylephrine is a direct acting alpha-adrenergic stimulator that causes vasoconstriction. The dose range is from 40 to 360 mcg/min. Norepinephrine stimulates alpha and beta adrenergic receptors, causing an increase in cardiac contractility and heart rate as well as vasoconstriction. Usual dosage is from 8 to 30 mcg/min. Vasopressin produces vasoconstriction by binding to V1 vascular receptors, not by catecholamine effect. The administration of vasopressor drugs to maintain blood pressure is useful to avoid the use of large volumes of IV fluid to compensate for anesthesia-induced vasodilation and cardiac depression. However, when the need for these drugs escalates, the anesthesiologist must reevaluate the patient's intravascular volume status because this is consistent with significant hypovolemia (see Table 24.6).

Pulmonary Complications

Intravascular volume resuscitation and the associated large fluid shifts caused by acute blood loss and multiple fluid and blood transfusions frequently produce significant airway edema. Not uncommonly the patient should remain intubated at the

Table 24.6 Vasopressors used during spine surgery

Drug	Receptor	Effect	Dose
Phenylephrine	Alpha 1	Vasoconstriction	40–360 mcg/min
Norepinephrine	Alpha 1, Beta 1	Vasoconstriction, increase cardiac contractility, may increase heart rate	0.2–3 mcg/kg/min Range 8–30 mcg/min
Ephedrine	Indirect alpha/beta	Vasoconstriction, increase cardiac contractility, may increase heart rate	5–25 mg/dose repeat after 5–10 min as needed
Vasopressin	V1	Vasoconstriction, may decrease cardiac output	0.01–0.04 units/min
Dopamine	Alpha, Beta 1, and dopamine	Vasoconstriction, increase cardiac contractility/heart rate	3–20 mcg/kg/min
Epinephrine	Alpha, Beta 1 and 2	Vasoconstriction (high dose), increase cardiac contractility/heart rate	1–10 mcg/min

end of the case until the airway edema clears, which occurred with our patient. A recent review of postoperative ventilation showed that following long, multilevel surgeries 44% of the patients were kept intubated overnight. These patients were older, had a higher ASA status, and their operations were longer with greater estimated blood loss (EBL). They received more IV crystalloid administration, the cases ended later in the day, and there was an increased number of attending anesthesiology handoffs. These patients also experienced more pneumonia (10.3% vs. 3.1%) [27].

Case Scenario (Continued)

Our patient had all of these risk factors and was sedated and ventilated overnight. He was successfully extubated the next morning after hemodynamic stabilization and resolution of airway edema.

Requirements for safe surgery:

- Large-bore IV cannulae in anticipation of massive blood loss and multiple drug infusion
- Arterial line for BP monitoring, blood sampling, and evaluation of postoperative respiratory function
- +/− CVP
- Monitors for CO_2 and arterial wave form analysis
- Fluid responsive monitors (e.g., TEE, PPV, esophageal Doppler, $EtCO_2$ elimination)
- Foley catheter if >2 h surgery is anticipated
- TIVA for neurophysiologic monitoring of SSEP and TcMEP for spinal cord injury
- Type and cross-match
- Coagulation monitoring with prothrombin time (PT), partial thromboplastin time (PTT), platelet count, and thromboelastrography (TEG).
- Postoperative analgesia plan

Postoperative Analgesia

The extent of the surgical procedure and the amount of narcotics consumed by the patient preoperatively dictate postoperative pain management. Narcotics decrease pain by central and spinal opiate receptor activation, but preoperative use can also produce tolerance. This must be taken into consideration when planning the postoperative analgesia regimen. There are many analgesic protocols including: intraoperative and postoperative narcotics, NSAIDS (use may be limited due to concerns for hematoma), low-dose ketamine, gabapentine, and lidocaine infusion.

Case Scenario (Continued)

Since our patient was on significant narcotic analgesics preoperatively, he received the aforementioned multimodal analgesia approach for postoperative pain management.

Postoperative Recovery

Our patient's postoperative course was complicated by extended intubation. There was a small rise in troponin level, which was from cardiac enzyme leakage due to an acute, short duration of intraoperative anemia, hypotension, and hypovolemia. The troponin elevation returned to normal over the next 2 days. He was discharged from the hospital in 4 days, after 2 days in the intensive care unit (ICU) for cardiac and pulmonary monitoring during intravascular volume equilibration. He did not experience any transfusion reactions and his pain was well controlled. He was discharged to a rehabilitation institution for physical therapy recovery and ongoing pain control.

Conclusion

Figures 24.1 and 24.2 summarize the importance of fluid management during major spine surgery. The optimal hemoglobin for oxygen delivery to major organs is between 9 and 11 g/dl in healthy patients. In those patients with cardiac, vascular, renal, and pulmonary disease the curve may shift to the right. With lower hemoglobin levels the oxygen-carrying capacity decreases, producing lower tissue

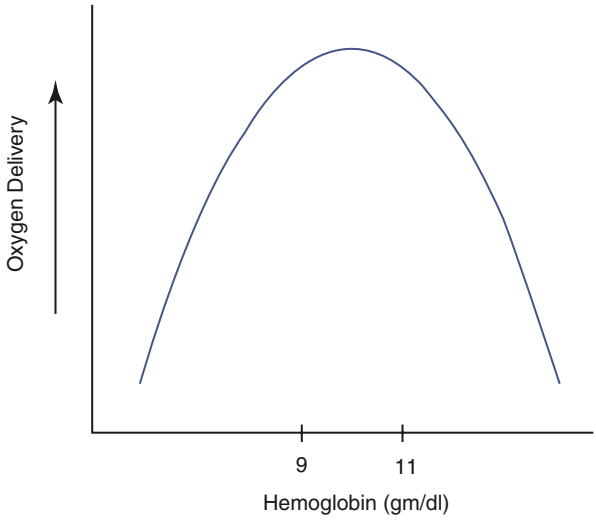

Fig. 24.1 Hemoglobin, oxygen delivery, and anemia

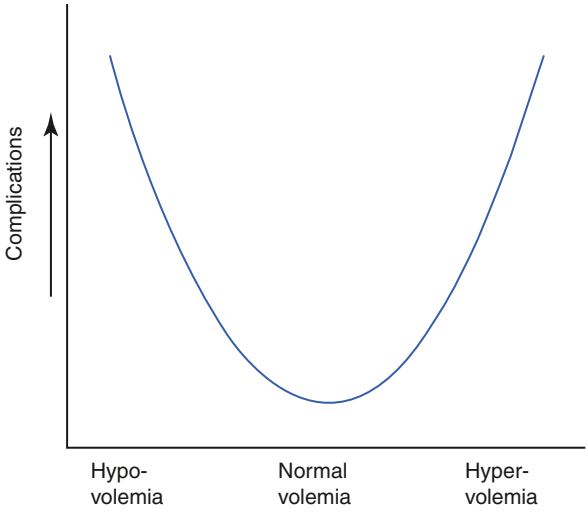

Fig. 24.2 Intravascular volume and complications

oxygenation. Greater hemoglobin levels progressively increase blood viscosity, which results in less oxygen delivery. Similarly, there is an optimal intravascular volume. The danger of hypovolemia is decreased tissue oxygenation and of hypervolemia is congestive heart failure and pulmonary edema. The combination of anemia and hypovolemia is an especially dangerous condition leading to tissue hypoxia, while overaggressive transfusion leads to hyperviscosity and volume overload. Fluid management for major spine surgery is essential for enhanced patient outcome.

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Case Scenario for Fluid Management After Subarachnoid Hemorrhage in the Neuro-Intensive Care Unit

25

Ibrahim Migdady, Jenny Peih-Chir Tsai, and Joao A. Gomes

Abstract

Subarachnoid hemorrhage is a cerebrovascular emergency with significant morbidity and mortality. The clinical presentation varies; most patients present with severe headache, nausea, vomiting and neck pain. Loss of consciousness can also happen in severe cases. Early diagnosis is essential and confirmed with a non-contrast CT of the brain with or without a lumbar puncture. The most common cause of nontraumatic subarachnoid hemorrhage is aneurysm rupture. Most patients with aneurysmal subarachnoid hemorrhage should be monitored closely in an intensive care unit after securing the aneurysm, to monitor for and prevent potential neurological and medical complications. Neurological complications include aneurysm rerupture, seizures, hydrocephalus, intracranial hypertension, and delayed cerebral ischemia, all of which can worsen outcome following subarachnoid hemorrhage. Systemic complications that can occur in these patients include acute cardiopulmonary decompensation (i.e. neurogenic pulmonary edema, estress cardiomyopathy, etc.), and hyponatremia secondary to cerebral salt wasting syndrome or syndrome of inappropriate antidiuretic hormone secretion. Close neurologic and hemodynamic monitoring and understanding of the pathophysiologic changes of this complex patient population is important to optimize patient outcome.

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Key Points

1. Subarachnoid hemorrhage is a neurological emergency that carries significant early and late neurological as well as medical complications.
2. Maintaining euvolemia rather than prophylactic triple H therapy is recommended to prevent cerebral ischemia.
3. Careful fluid administration and induced hypertension are the traditional mainstays of treatment of aneurysmal subarachnoid hemorrhage (SAH) patients who develop cerebral vasospasm. Goal-directed fluid therapy (GDFT) can assist in optimizing cerebral perfusion in affected patients. Empiric induced hypertension, hypervolemia and hemodilution ("Triple H therapy") is not recommended. Use of intra-arterial and/or intrathecal vasodilators and balloon angioplasty complement the therapeutic arsenal in these patients.
4. Patients with high-grade SAH are at risk of stunned myocardium. Timely recognition of cardiopulmonary sequelae of high-grade SAH is important for appropriate fluid management.
5. Hyponatremia in SAH patients carries additional risk for morbidity and mortality. The two common etiologies are syndrome of inappropriate antidiuretic hormone and cerebral salt wasting. Avoiding and correcting hypovolemia and hyponatremia is key to optimize clinical outcomes.

Introduction

Subarachnoid hemorrhage (SAH) is a devastating neurological emergency with an overall mortality of 40–67% [1, 2]. Half of the affected patients will die within 2 weeks of the ictus, including 12% who die prior to hospital arrival, and another 20% left with significant functional and cognitive disability [3, 4]. The initial hemorrhage has direct and secondary neurological effects in the early and late course of the illness such as re-bleeding, seizures, hydrocephalus, and delayed cerebral ischemia (DCI)with or without cerebral vasospasm. Multisystem complications are common in SAH patients, who are at risk for cardiac, pulmonary, renal, endocrine, and infectious complications. The presenting clinical severity of the initial ictus along with the potential secondary neurological and systemic sequelae necessitate close monitoring of these patients in an intensive care unit (ICU) to minimize morbidity and mortality [5]. Judicious management of fluid and electrolyte status is central to optimizing patient outcome.

Case Scenario

A 61-year-old man with a past medical history of hypertension, and tobacco use presented to the emergency department (ED) with sudden onset of severe bi-frontal headache associated with nausea, vomiting, meningismus, and confusion. There was no history of sentinel headache, trauma, or antithrombotic use. In the ED, his mental status deteriorated from drowsiness to obtundation. He was intubated for

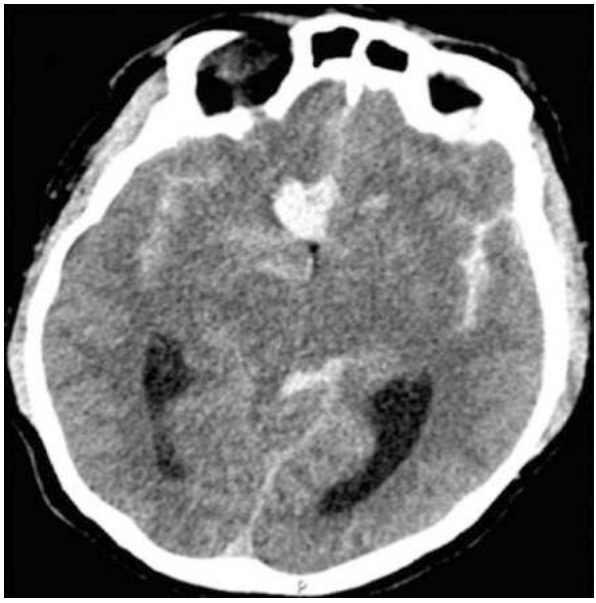

Fig. 25.1 Computed tomography brain scan without contrast showing diffuse thick SAH with IVH and early hydrocephalus

airway protection. Computed tomography (CT) scan of the brain without contrast revealed diffuse and thick basal cistern subarachnoid hemorrhage with intraventricular extension and evidence of early hydrocephalus as shown in Fig. 25.1. His initial blood pressure (BP) was 195/112 mmHg. Initial laboratory testing showed normal plasma sodium, other electrolytes, and creatine levels, and normal coagulation parameters and platelet count.

What is the best initial approach in this patient's evaluation and management?

Discussion

General Approach To Subarachnoid Hemorrhage.

Severe, sudden-onset or "thunderclap" headache is the most common presenting symptom of SAH, classically described as the "worst headache of one's life". In 30% of patients whose SAH are aneurysmal in etiology, the headache may be lateralized to the side of the aneurysm [6]. Similar to other medical emergencies, the first step in managing patients with suspected SAH is ensuring intact airway, breathing and circulation. Altered level of consciousness, hemodynamic instability, and cardiorespiratory failure may be present at onset and require aggressive resuscitation. Noncontrast CT of the head is the initial diagnostic test of choice in patients with suspected SAH, with a sensitivity of ≥95% within 6 h of hemorrhage [7–11]. With newer generations of CT scanners, the sensitivity is 98.5% for detection of SAH within 6 h, with specificity and positive predictive value of essentially 100% in patients presenting with typical thunderclap headaches [11]. In addition to SAH, noncontrast CT may demonstrate early hydrocephalus in approximately 20–30% of

patients who survive the initial 24 h post hemorrhage [12–14]. These patients typically benefit from external cerebrospinal fluid (CSF) drainage. Cerebrovascular imaging through noninvasive modalities, such as CT or magnetic resonance imaging (MRI), or catheter angiography, should be obtained early to identify the etiology of SAH.Other notable etiologies of SAH include trauma (most common etiology overall), ruptured arteriovenous malformations or fistulae, venous hemorrhages, intradural dissection, cerebral amyloid angiopathy, and anticoagulant-associated hemorrhages; these entities are beyond the scope this review. However, it is important to note that initial approach to patients with subarachnoid hemorrhage of aneurysmal versus non-aneurysmal etiology is similar in concept, but their management may soon divergedue to differing natural histories including risks of hydrocephalus and secondary injuries; this discussion focuses on SAH secondary to ruptured cerebral aneurysms [15, 16]. In patients with aneurysmal SAH (aASH), early arterial blood pressure (BP) and goal-directed fluid management are paramount: though recent advances in diagnosis and management have resulted in improved outcomes, a significant proportion of patients who survive the initial event will develop severe morbidity or mortality due to secondary neurological or systemic complications [1, 2, 17]. An immediate neurosurgical evaluation should also follow the diagnosis of aSAH to definitively secure the source of hemorrhage, due to a 72-hour re-bleeding risk as high as 5 to 10% [18].

The patient was placed on NPO status, and weight-based maintenance isotonic fluid infusion was initiated, targeting intravascular euvolemia. An arterial line was inserted for on-going blood pressure monitoring and management. The neurosurgical team was consulted, and an external ventricular drain (EVD) was placed. CT angiography (CTA) of the head revealed an anterior communicating artery aneurysm, which was successfully treated endovascularly through primary coil embolization within the same day. He was then transferred to the neurological intensive care unit (NeuroICU) for further monitoring and management, including placement of non-invasive monitors of hemodynamic parameters as well as performance of bedside lung and cardiac point-of-care ultrasound (Fig. 25.2).

Upon admission to the NeuroICU, the patient's BP was 174/90 mmHg, and blood pressure reduction with a continuous nicardipine drip was initiated. Repeat neurologic assessment off sedation revealed equal and reactive pupillary responses to light, cornea, with present cough and gag reflexes, and bilateral upper and lower extremity withdrawal to midline noxious stimuli.

What are early complications of aneurysmal SAH that may impact fluid management and what are the appropriate prophylactic or treatment strategies?

Early complications of aneurysmal subarachnoid hemorrhages with impact on fluid management include intracranial hypertension, stress cardiomyopathy (i.e. Takotsubo), hyponatremia, neurogenic pulmonary edema, and delayed cerebral ischemia.

The expected clinical course following a SAH relates back to the initial clinical presentation. Several clinical grading scales have been proposed, and the most commonly used are the Hunt and Hess and the World Federation of Neurosurgery Scales, which provide prognostic indicators for the patient's ultimate outcome

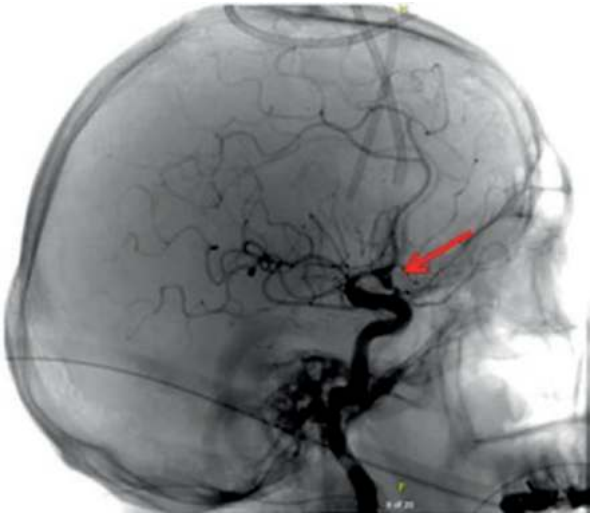

Fig. 25.2 Cerebral angiogram shows a large saccular aneurysm in the supraclinoid segment of the internal carotid artery (red arrows), measuring 11 mm × 8 mm × 9 mm. Irregularities may indicate a pseudoaneurysmal component in the wall, and are associated with either recent rupture or increased risk of hemorrhage

Table 25.1 The Hunt and Hess and World Federation of Neurosurgery (WFNS) clinical subarachnoid severity grading scales

Grade	Hunt and Hess	World federation of neurosurgery
1	Asymptomatic or mild headache and slight nuchal rigidity	GCS 15 No motor deficits
2	No neurological deficit except cranial nerve palsy, moderate to severe headache, nuchal rigidity	GCS 14–13 No motor deficits
3	Drowsiness or confusion or mild focal deficit	GCS 14–13 Motor deficits
4	Stupor, moderate to severe hemiparesis	GCS 12–7 With/without motor deficits
5	Deep coma, decerebrate posturing, moribund appearance	GCS 6–3 With/without motor deficits

GCS Glasgow Coma Scale

[19–21] (Table 25.1). The Modified Fisher Scale (mFS) is a commonly used radiological severity grading scale, and primarily predicts the risks of cerebral vasospasm. The mFS is based on the thickness of the subarachnoid hemorrhage and the presence or absence of intraventricular hemorrhage extension on the initial noncontrasted head CT [22] (Table 25.2).

Intracranial hypertension due to hydrocephalus, cerebral edema, mass effect, etc., can arise at any time following aSAH, from an acute onset to a delayed presentation days to weeks after the index event [23–25]. High-grade SAH, denoting a larger amount of subarachnoid blood, and the presence of intraventricular hemorrhage (IVH) are associated with increased risk of developing acute obstructive hydrocephalus, which in turn is an independent risk factor for worse outcomes

Table 25.2 The modified fisher scale

Grade	CT findings descriptions
0	No subarachnoid hemorrhage
1	Thin cisternal subarachnoid hemorrhage without intraventricular hemorrhage
2	Thin cisternal subarachnoid hemorrhage with intraventricular hemorrhage
3	Thick cisternal subarachnoid hemorrhage without intraventricular hemorrhage
4	Thick cisternal subarachnoid hemorrhage with intraventricular hemorrhage

CT computed tomography

[26]. While systemic fluid volume status typically does not directly impact intracranial pressure due to the presence of the blood-brain barrier (BBB), BBB disruption is common following aSAH and over resuscitation, particularly with hypotonic fluids can be detrimental. A close relationship exists between the intracranial pressure (ICP), serum osmolality and acid-base balance, and arterial pressure. In the context of acute rise in intracranial pressure, the primary resuscitative goals are the maintenance of cerebral perfusion pressure (CPP) and the avoidance of cerebral herniation. Therefore, cerebral perfusion pressure's defining formula as the difference between the mean arterial pressure (MAP) and the ICP, in conjunction with the well-recognized Monro-Kellie doctrine's estimated relative intracranial compartments' volumes, drives the rationale for both fluid and blood pressure managements in this acute setting. Initial management of emergent intracranial hypertension relies on medical optimization of intracranial fluid volume shifts. This can be achieved with head-of-bed elevation and neck straightening for adequate venous drainage; use of hypertonic intravenous solutions for osmotic shift of cerebral extracellular fluid to the intravascular space; transient hyperventilation to an arterial CO_2 level of 25 to 35 mmHg to reductions in cerebral blood volume; maintenance of normothermia; sedation, etc. When administered as a bolus, hypertonic solutions can provide a rapid relief in intracranial pressure. Hypertonicity can be achieved with either sodium or mannitol as active osmotic agents. Hypertonic saline is available as multiple formulations, and most commonly as 2%, 3% and 23% buffered saline solutions. Available mannitol concentrations range from 5 to 20%, and can similarly effect a near-immediate drop in ICP in situations of emergent intracranial hypertension. However, due to mannitol's minimal (less than 10%) renal tubular reabsorption, cautious monitoring of systemic intravascular volume is warranted as significant hypovolemia may subsequently result from its delayed osmotic diuretic effect and require repletion to euvolemia. In addition, plasma sodium and osmolality should be monitored over the hours subsequent to the administration of hypertonic solutions. Serum osmolality should be maintained at less than 320 mOsm, and plasma sodiumat least within the normal range, if not up to 160 meq/L depending on desired effect. It is important to underline that the use of hypertonic fluids in this context is for emergent and temporizing management of intracranial hypertension only; immediate placement of an EVD is both critical and lifesaving. In the setting of acute hydrocephalus secondary to SAH, the EVD allows for ICP monitoring and therapeutic drainage of CSF.

Aneurysmal SAH patients can present with various cardiac complications ranging from non-specific electrocardiogram (EKG) changes to a severe form of cardiac injury known as neurogenic stunned myocardium or Takotsubo cardiomyopathy [27]. This phenomenon is postulated to result due to a neurologically mediated sympathetic surge that leads to excessive catecholamine release following acute SAH and high ICP. The subsequent endocardial damage can lead to a stunned myocardium, which can present with cardiogenic shock. Typically, low ejection fractions are detected on transthoracic echocardiogram (TTE), and may demonstrate improvement within one week on repeat echocardiogram [28]. Cardiac enzymes can be mildly elevated, differentiating the clinical presentation from an acute myocardial infarction. Sequential repeat levels tend to normalize alongside cardiac function [29, 30]. Thus, admission EKG, cardiac enzymes, and a TTE are important to detect and manage such complications, which in turn warrant judicious fluid management in accordance with the patient's cardiac function. Trending relevant hemodynamic parameters (i.e. stroke volume, cardiac output, stroke volume variability), which can be obtained with minimally invasive technology, and the use of bedside point of care lung and cardiac ultrasound can also aid in the management of these patients.

Our patient's clinical presentation and radiological findings were classified as Hunt and Hess grade 4, modified Fisher grade 4, respectively. He had signs of hydrocephalus on his CT brain scan for which he initially underwent EVD placement with normal opening pressure and normal subsequent ICP readings. EKG showed normal sinus rhythm with non-specific ST-T changes and the first set of cardiac enzymes were within normal limits. Then, on post-bleed day 5, the patient's hourly urine output increased by 2 to 3 times. Meanwhile, his sodium level dropped from 141 mmol/L to 133 mmol/L over 12 h.

What is the next step in the evaluation of his hyponatremia? What is its significance in SAH patients? How would you manage his hyponatremia?

Hyponatremia is defined as sodium (Na) level < 135 mmol/L. It is the most common electrolyte derangement in patients with SAH, with an incidence of approximately 30–40% [31–33]. Hyponatremia in SAH patients is associated with increased risk of cerebral edema. The most common subtype of hyponatremia in this setting is hypotonic hyponatremia, notably due to **cerebral salt wasting**. Syndrome of inappropriate antidiuretic hormone secretion (SIADH), can occur much less frequently. The pathophysiology of both syndromes is not entirely understood and their differentiation can at times be challenging [34]. It is important to distinguish between these causes of hyponatremia in patients with SAH, as the inappropriate treatment may not only fail to correct but may also worsen the patient's volume and electrolyte status. However, appropriate initial diagnosis can be challenging due to several overlaps in the patient's clinical and laboratory features [23]. Both syndromes are characterized by a low serum osmolality (<285 mOsm/kg), high urine osmolality (>200 mOsm/kg), high urine sodium concentration (>40 mmol/L) and decreased serum uric acid levels.

Cerebral salt wasting is a hypotonic hyponatremia, generally associated with hypovolemia. It is a centrally-induced salt-wasting nephropathy postulated to occur secondary to either impaired sympathetic input to the kidneys, or secondary to

release of brain natriuretic peptide (BNP) in response to cerebral injury or intracranial hypertension, with or without direct insult to the hypothalamus, and subsequent suppression of the renin-aldosterone-angiotensin system [35]. Cerebral salt wasting is more commonly noted in conjunction with high clinical grade SAH, ruptured anterior communicating artery aneurysms, and hydrocephalus [36, 37]. In patients with cerebral salt wasting, decreased sodium reabsorption occurs at the level of the proximal renal tubule [38]. While decreased renal tubular sodium reabsorption is also a key pathophysiological step in SIADH that leads to natriuresis, the relatively abnormal ADH level leads to distal tubular water reabsorption, and results in euvolemia or hypervolemia in some patients. A potentially complicating but important factor in the diagnosis of CSW versus SIADH in the SAH patient, is that hypovolemia in CSW can be so profound that it secondarily stimulates ADH release, resulting in a mixed pathophysiology best corrected through careful treatment of CSW [35].

Though seemingly intuitive, a first step in the workup of hyponatremia in all critically ill neurological patients is to confirm that the reported drop in sodium level is neither a laboratory error nor pseudohyponatremia. Important laboratory parameters include simultaneously measured serum and urine sodium and osmolality. Pseudohyponatremia occurs when there is an apparently but falsely low sodium level in a setting of normal or high plasma osmolality (≥285 mOsm/kg). Hyperglycemia and hypertriglyceridemia will result in pseudohyponatremia with normal osmolality, while the presence of another effective osmole, such as mannitol, many account for a high osmolality [39].

Once true hyponatremia is confirmed, the next step in clinical evaluation is to correctly identify patient's volume status, as it is the key distinguishing feature between CSW and SIADH [40]. Assessing a patient's fluid status can be challenging, and begins with physical examination. Signs suggestive of low volume status include decreased skin turgor, cool extremities, oliguria, and hypotension. There is no validated single or gold standard measure for accurate volume status assessment; it is typically estimated through a combination of invasive or noninvasive methods. Hourly accurate measurements of input and output through an indwelling catheter are important. Free water balance and sodium deficits can be estimated with known fluid in-and-out measurements, with care to account for sensible and insensible losses [41–43]. Daily weight measurements can also estimate variations in the patient's volume status. Central venous pressure (CVP) can serve as another adjunctive measurement to guide fluid management, though its reliability in estimating intravascular volume status is limited due to additional determinants, including right-sided cardiac function, pulmonary circulation and intrathoracic pressures, and mechanical ventilation parameters [44]. Inferior vena cava distensibility can be assessed by point-of-care ultrasound, and is also a useful adjunct to assess fluid status and responsiveness, as can the passive leg raise maneuver and an elevated stroke volume variability [45, 46]. Pulmonary wedge pressures (PWP) measured through pulmonary artery (PA) catheters may have a role in hemodynamically unstable SAH patients, particularly in those with prominent right-sided heart failure, even though PA catheter insertion carries significant risks that may outweigh their benefits [5, 47].

Following a thorough evaluation, hyponatremia should be corrected in accordance with the working diagnosis of the causative syndrome. Timely treatment is important, as a precipitous drop in sodium, particularly with severe (<110 mEq/L) hyponatremia, can result in new-onset seizures in approximately 30% of patients [48]. This is of particular consideration in the SAH population, as seizures are reported in up to 26% of patients, and have been independently associated with worse outcome [49, 50]. Care must be taken in gradual correction of hyponatremia with frequent monitoring, since a rapid correction can lead to the development of osmotic demyelination syndrome [51]. We recommend monitoring sodium levels every 4 to 6 h after initiating treatment. Correction should occur at a rate no greater than 1–2 mEq/L/h, and no more than 8–10 mEq/L in the first 24 h [43]. A sliding scale approach may provide practical benefit in titrating treatment at the point of care [52].

Two principles are key to fluid choices in the correction of hyponatremia in SAH patients. First, as these patients are at risk of cerebral ischemia, hypovolemia should be absolutely avoided. Therefore, SIADH in an aSAH patient should never be treated with fluid restriction [53]. Second, as CSW is characterized by a hypovolemic state where extracellular volume depletion is in excess of sodium deficit, the initial phase of treatment should aim to replete both total body water and sodium [35].

In patients with CSW, administration of isotonic fluid with normal saline or hypertonic saline solutions is therefore a sound initial treatment strategy, as even isotonic saline solutions have a higher sodium concentration (154 mEq/L) than the hyponatremic patient's plasma [35]. It is important to note that sodium level may rise more dramatically than expected in those volume-depleted CSW patients who also have a relatively elevated ADH level upon initial volume resuscitation, which can result in a rapid overcorrection. Close monitoring of intravascular volume status and plasma sodium level, and judicious adjustments in fluid tonicity, volume, and rate, are therefore paramount. Despite the general approach to first correct hypovolemia, since isotonic saline results in a slower sodium correction than can achieved with hypertonic solutions, the latter may be a preferred initial treatment strategy in patients with severe hyponatremia. Limited data associates 3% hypertonic saline in CSW in patients with high-grade SAH with improvement in regional cerebral blood flow (CBF) and partial pressure of brain tissue oxygen tension. However, no similar studies have compared its effectiveness versus normal saline, or the physiologic effect of intravascular volume and plasma sodium normalization [54, 55]. Evidence in support of routine albumin use for volume expansion and maintenance of euvolemia or hypervolemia in all SAH patients is scant, though existing data and experience extrapolated from non-SAH populations suggest that both hypertonic saline and albumin infusions are relatively safe [56].

Other than fluid administration, mineralocorticoid therapy may be considered for patients with CSW. Given the suppression of the renin-angiotensin-aldosterone system, addition of a mineralocorticoid is expected to increase renal sodium retention. In patients with CSW secondary to SAH, adjunctive fludrocortisone is associated with reduced natriures is and cerebral vasospasm and reducing the amount of fluid required to achieve euvolemia [57, 58]. However, combined fluid and

fludrocortisone therapy can result in a rapid rise in sodium level while increasing the risk of hypokalemia and hyperglycemia. Caution is therefore warranted. Despite their effectiveness in correcting hyponatremia in CSW, a recent systematic review of randomized controlled trials on the use of mineralocorticoids failed to demonstrate definitive benefit in functional outcomes [59].

In patients with SAH complicated by SIADH, fluid restriction is **never** recommended. Normal saline infusion can worsen hyponatremia in SIADH as urine osmolality is typically higher than the isotonic fluid, which can expand intravascular volume and stimulate further ADH secretion. Hypertonic saline is likely a more effective therapy in SAH patients with SIADH [5, 56]. Oral salt tablets can be added to help promote urine output and to raise sodium levels, are available in 1 to 2 g tablets, and can be dosed up to three times a day [52]. However, the achievable replacement dose with oral tablets is modest in comparison with intravenous fluids, as each gram provides only 17 mEq of sodium, and the taste of sodium tablets can be difficult to tolerate when taken by an oral route. Vasopressin receptors 2 (V2R) antagonists, such as conivaptan, promote aquares is and may adjunctively raise the sodium level, especially in severe symptomatic hyponatremia. This may be useful in the SAH patient who is volume overloaded and hyponatremic. Caution should again be exerted to avoid rapid rise of sodium levels with use of V2R antagonists [60].

Though less common than hyponatremia, SAH patients may also present with hypernatremia due to diabetes insipidus (DI) [61]. An acute, post-SAH incidence of DI of up to 15% has been reported [36]. Posterior pituitary dysfunction secondary to acute intracranial hypertension is postulated as the likely etiology in most of the affected patients [61]. Perforator artery injury secondary to surgical clipping of anterior communicating artery aneurysms may also rarely cause adipsic DI [62–65]. The appropriate treatment is with desmopressin, dosed per the severity of DI and titrated per routine plasma sodium concentration checks, and with additional regular oral or parenteral fluid replacement per estimated lossin patients with adipsic DI [66]. A trend towards normalization is expected as patients recover, with a drop in prevalence of DI in SAH patients to only 2.8% at 12 months [67].

Lastly, eunatremia in conjunction with new-onset polyuria also warrants close clinical attention, as it can be a harbinger of cerebral vasospasm. In one study, up to 45% of patients with new-onset polyuria developed cerebral vasospasm shortly after, despite adequate volume replacement and persistent eunatremia. Significant association between eunatremic polyuria and cerebral vasospasm was reported after adjusting for age, hypertonic solution use, ventriculostomy, and clinical and radiographic severity scores [68].

On post-bleed day 7, the patient's neurological exam deteriorated from bilateral upper and lower extremity withdrawal to bilateral decorticate (flexor) response to noxious stimuli. A repeat head CT revealed stable hemorrhage burden and ventricular sizes. Bedside monitoring parameters remains within normal: arterial blood pressure was 138/67 mmHg, with a mean (MAP) of 91 mmHg, and intracranial pressure readings recorded through the EVD ranged from 6–14 cm H_2O. His daily transcranial Doppler (TCD) readings revealed elevated mean flow velocities (MFV) in his bilateral middle cerebral arteries (MCA), exceeding 200 cm/s, both increased from less than 140 cm/s the day prior. Off sedation, continuous electro

encephalography revealed diffuse and non-lateralizing slowing of the brain in the delta range without epileptiform activities to suggest subclinical seizures.

What is the likely cause of the new neurological exam worsening? What is the optimal management strategy?

The change in the patient's neurological exam, in correlation with the elevation inflow velocities on transcranial doppler (TCD) monitoring, is likely secondary to delayed cerebral ischemia, with cerebral vasospasm.

Delayed cerebral ischemia (DCI) is the top differential diagnosis for neurological deterioration within days following subarachnoid hemorrhage, especially when associated with focal deficits. Timely diagnosis and initiation of appropriate management are important, as cerebral ischemia after aneurysm a SAH is usually a treatable secondary injury process.

Most commonly occurring between 4 and 14 days, with a peak incidence approximately one week after SAH, cerebral vasospasm and DCI are terms that refers to two distinct but overlapping concepts related to the complex ischemic pathophysiological process precipitated by the index hemorrhage [69, 70]. Cerebral vasospasm is best defined as radiographic narrowing of cerebral vasculature that is reactive in nature. Delayed cerebral ischemia defines either the clinical or radiographic evidence of tissue ischemia [70, 71]. Though vasospasm can be associated with DCI, they are neither mutually exclusive nor reliably predictive of one another. Whereas 50–60% of SAH patients develop cerebral vasospasm, less than half of patients with moderate to severe vasospasm develop clinical or radiographic evidence of significant hypoperfusion or infarction. Meanwhile, DCI occurs in approximately 30% of patients and does not always colocalize with the observed vascular narrowing. DCI likely results from a complex pathophysiology involving several mechanisms such as cerebrovascular dysfunction, microcirculatory thrombosis, cortical spreading depolarization, neuroinflammation, oxidative stress, and iron toxicity among others [72]. Cerebral vasospasm can be considered a macrovascular manifestation of cerebrovascular dysfunction, alongside loss of autoregulation, endothelial dysfunction, neurovascular decoupling, altered blood-brain barrier permeability, and smooth muscle proliferation. Overall, DCI is a major cause of morbidity and mortality following subarachnoid hemorrhage [73].

Risk factors for cerebral vasospasm include history of tobacco and alcohol use, hyperglycemia, hydrocephalus, poor clinical status at presentation, and higher burden of hemorrhage in the basilar cistern, in proximity to the Circle of Willis [74]. The expected clinical manifestations of DCI sometimes reflect the vascular territory of the affected arterial distribution, and can range from focal neurological deficits or global change in the level of consciousness.

Diagnosis and Treatment Effect Monitoring

Despite the distinguishing features between cerebral vasospasm and DCI, clinical monitoring and management for these entities are largely identical. All patients admitted with aneurysmal SAH should be closely monitored for cerebral vasospasm and DCI, particularly those with risk factors. In addition to frequent routine

neurological examinations, various adjunctive monitoring techniques for early detection of DCI are available. The most common one is daily transcranial Doppler study (TCD) throughout the period where the patient is at highest risk for vasospasm. TCD provides a bedside noninvasive and generally well-tolerated monitoring of flow velocity trends and variations in the proximal intracranial arteries in both anterior and the posterior circulations. Accounting for operator-dependent variabilities and the patient's sonographic windows, TCD demonstrates good sensitivity and specificity as compared to conventional angiography for early detection of vasospasm, although results need to be interpreted with caution [75–77]. Of note, TCD is less accurate for prediction and monitoring for DCI than for vasospasm [78]. Digital subtraction angiography (DSA) is considered the gold standard for detection of vasospasm, and provide the possibility of intra-arterial therapy in case of severe and/or refractory vasospasm [79]. CT angiography and perfusion imaging can also be useful non-invasive adjunctive imaging modalities. Non-vascular adjuncts for monitoring for DCI also exist. Continuous electroencephalography (cEEG) monitoring may help in early detection of DCI, especially in comatose patients whose serial neurologic examination provides limited guidance in clinical management [14–17]. Invasive monitoring of cerebral oximetry and metabolism with microdialysis measurements are also adjunctive means to assess cerebral perfusion in DCI, and can provide useful additional information when delivering hemodynamic augmentation therapy in at-risk patients [80]. However, due to variabilities in interpretations based on sampling sites, and the delayed data output, there is still insufficient evidence to recommend its routine use in all SAH patients [79, 80]. Multimodal monitoring is an active area of research is this particularly vulnerable patient population.

Treatment of Cerebral Vasospasm and Delayed Cerebral Ischemia.

Oral **nimodipine** is recommended for all SAH patients on admission for aneurysm rupture, and continued for 21 days, as *prophylaxis* for delayed cerebral ischemia [81]. Oral nimodipine does not affect radiographic vasospasm but is associated with improved overall clinical outcomes. The mechanism of this effect remains unclear but is postulated to be due to direct neuroprotection [82]. While the standard dosing is 60 mg every 6 h, drops in blood pressure are commonly observed shortly after oral nimodipine administration. These periodic troughs in systemic blood pressure can potentially decrease the patient's cerebral perfusion pressure (CPP). In the affected patients, a trial of nimodipine dosing change to 30 mg every 2 h is likely the simplest solution in ensuring stable hemodynamic parameters. In some instances, nimodipine may need to be discontinued or vasopressors added to support the patient's blood pressure.

Despite the common use of nimodipine, and given the multifactorial nature of DCI, no single treatment is currently known to completely reverse its pathophysiology, and cerebral vasospasm remains the best recognized process amenable to intervention. In patients with suspected vasospasm or DCI, prompt intravascular volume expansion and blood pressure augmentation may provide initial improvement incerebral blood flow pending radiographic confirmation of vasospasm.

Avoidance of hypovolemia and timely diagnosis of cerebral vasospasm are crucial in aSAH patients. Hypovolemia is associated with higher incidence of cerebral

infarcts and worse outcomes in aSAH patients [12]. The optimal intravascular volume status is euvolemia; prophylactic "triple H therapy"(hypertension, hypervolemia, and hemodilution) is not recommended [81]. In aSAH patients, hypervolemia shows no benefit as measured by cerebral blood flow (CBF), cerebral oxygen delivery, TCD-defined vasospasm, or clinical outcome when compared to euvolemia, while increasing the risk of systemic complications [83–86] (i.e. Michelin Man syndrome).

However, avoidance of hypervolemia does not negate the role of active fluid status management. Normal saline bolus and cautious, transient intravascular volume expansion is a reasonable first intervention as it has been shown to raise CBF in regions of the brain that are most vulnerable to ischemia [87]. Fluid administration should be a judicious process, especially in patients with decreased left ventricular systolic function, and with careful watch for hyperchloremic metabolic acidosis [88]. Goal-directed fluid management (GDFM) can improve clinical outcomes and prevent DCI in patients with subarachnoid hemorrhage, with particular benefit noted in patients with high-grade SAH and undergoing surgical aneurysm clipping [89, 90]. The use of cardiac output (CO), arterial pulse pressure variations (PPV), and stroke volume variation (SVV) as dynamic means to estimate CBF and cerebral oxygen delivery, can now be performed without the need of invasive physiologic monitoringand should be routinely used in most patients. These parameters are accurate predictors of fluid responsiveness except in patients with spontaneous breathing, cardiac arrhythmia, and right ventricular failure [91, 92].

Lactated Ringer's or colloid infusions can be helpful alternatives to normal saline in managing fluid status in patients with cerebral vasospasm, with obvious caution to avoid hyponatremia when using balanced solutions. Albumin at higher doses appears well tolerated in SAH patients and may be associated with lower risk of vasospasm [93]. Hypoalbuminemia has also been associated with higher incidence of new neurological deficits in post-SAH patients [94].

Similarly, anemia has been associated with poor outcome after SAH: A fall in hematocrit count and anemia leads to lower arterial oxygen content, thus decreases in cerebral oxygen delivery put patients at higher risk for DCI and poor outcome. This concept led to abandoning the practice of hemodilution [95]. Transfusion of packed red blood cells (PRBC) can improve cerebral oxygen delivery in anemic patients. Although there is no consensus on a target hemoglobin or hematocrit, a general practice recommendation suggests levels above 8 to 10 g/dL, with one study showing safety of targeting a higher value of 11.5 g/dL in SAH patients at particular risk of vasospasm [96].

Hemodynamic augmentation through induced hypertension is the current mainstay of non-invasive DCI management. The goal is to improve cerebral perfusion pressure (CPP), normally calculated as the difference between mean arterial pressure (MAP) and ICP. However, in disease states such as hemodynamically significant cerebral vasospasm, the loss of autoregulation and the elevated intravascular resistance override the effect of ICP, as a result of which CPP becomes passive and dependent on the MAP. Induced hypertension is commonly achieved by either norepinephrine or phenylephrine infusions. Vasopressor infusions should be titrated

either to a percentage increase in MAP, or in step-wise increments to a specific target. Inotropes increase cardiac output, and can be especially useful in patients with high-grade SAH that developed neurogenic stunned myocardium and low ejection fraction [97]. Milrinone is a selective phosphodiesterase 3 inhibitor with a direct vasodilator effect and positive ionotropic properties. Intravenous and intrathecal milrinone have become a successful emerging therapies for cerebral vasospasm and DCI in SAH with promising results, making it standard of therapy for refractory cerebral vasospasm in some institutions [98–100]. Systemic milrinone should be used cautiously in patients with severe hypotension. Milrinone-induced hypotension can be countered with concomitant phenylephrine or norepinephrine [101].

Endovascular therapy is the next step in the treatment of cerebral vasospasm. It includes intra-arterial infusion of a calcium channel blocker, and angioplasty of large and proximal cerebral arteries with severe, flow-limiting, and refractory vasospasm. While refractory cerebral vasospasm may require repeat endovascular interventions, it can still be associated with favorable outcomes [102]. Otherwise, the use of intra-aortic balloon pump counter pulsation (IABP) has been reported to assist with management of high-grade SAH with cardiac dysfunction and neurogenic stunned myocardium at high risk of significant morbidity from cardiopulmonary decompensation [97, 103].

The Neurointerventional team was notified of possible need for urgent intervention, as patient underwent immediate blood pressure augmentation, and one liter of normal saline bolus with initiation of Norephinephrine drip, which was titrated to improvement in his neurological status. Follow-up exam returned to withdrawal to noxious central stimuli once MAP was sustained above 110 mmHg. He was urgently taken to the angiography suite. DSA showed evidence of moderate to severe cerebral vasospasm with moderate flow limitation in bilateral supraclinoid internal carotid arteries, and bilateral middle and anterior cerebral artery (ACA) territories. Intra-arterial verapamil infusion demonstrated some improvement in arterial filling and overall transit time. The patient returned to the Neurocritical Care Unit for ongoing management [104, 105].

Conclusion

Secondary injury processes in the hyperacute through subacute periods after aneurysmal subarachnoid hemorrhage require judicious fluid management strategies. The risks for intracranial hypertension, cardiopulmonary dysfunction, sodium dysregulation, and delayed cerebral ischemia warrant careful maintenance of euvolemia while titrating to hemodynamic and electrolyte parameters appropriate to the patient's evolving neurological and systemic status through the course of recovery. With thorough understanding of the pathophysiology involved and with apt interpretations of available multimodal monitoring data, fluid management can be fine-tuned to support the patient through this challenging disease.

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Case Scenario for Fluid Management in Cardio-Thoracic Surgery

26

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Abstract

Fluids administration should aim at restoring normovolemia. Dynamic indices, such as pulse pressure variation or systolic pressure variation are far better than static pressure measurements, such as central venous pressure. Even if dynamic indices indicate a fluid-responsive state, fluids should not be administered if hemodynamics are stable. The clinical application of dynamic perfusion indices is unknown in the presence of sternotomy and thoracotomy.

Key Points

- The clinical goal is to optimize cardiac output and perfusion (or, increase mixed venous oxygen saturation, decrease lactate).
- Mortality and major morbidity are not affected by a restrictive or liberal transfusion practice.
- The type of volume expansion (crystalloids, albumin, blood) should be individualized.
- Intravenous fluids are indicated in hypotension if indexed stroke volume (SV_i) is decreased or pulse pressure variation (PPV) is increased and cardiac function is preserved (or supported).
- Ventilation-induced phasic changes of venous return to the ventricles and pulmonary and chest wall compliance affect all catheter-based hemodynamic measurements (central venous pressure, pulmonary artery occlusion pressure, blood pressure and variations).

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- Pressure-based, static indicators of preload (central venous pressure, pulmonary artery occlusion pressure) are inaccurate in predicting volume responsiveness and should not be used to guide volume loading.
- Dynamic indices (systolic pressure, pulse pressure) are better predictors of volume responsiveness but have important limitations. They require closed chest setting, mechanical ventilation (most are validated at tidal volume > 8 ml/kg) and normal, not tachycardia, rhythms.
- Fluid-responsiveness alone, as indicated by dynamic indices, is not a reason for volume administration.

Case Scenario

A 78 year old female is diagnosed with a bicuspid aortic valve and ascending aorta aneurysm. Accelerated growth of the aortic diameter along with moderate aortic stenosis prompt elective aortic root surgery and aortic valve replacement. The patient is otherwise healthy and preserved left ventricular ejection fraction. Her preoperative hematocrit (Hct) is 38%. During huddle, the team decides to monitor her intra- and postoperatively with invasive arterial and central venous lines and intraoperative transesophageal echocardiography. No pulmonary artery catheter will be used.

Questions

- Is there a "valid" transfusion trigger?
- What should be the hemodynamic goals?
- When is intravenous (i.v.) volume expansion indicated?
- How is fluid responsiveness measured?
- Should i.v. fluids administered if patient is found to be fluid responsive?

Discussion

Transfusion Triggers

Nowadays, the transfusion thresholds ("triggers") for red blood cell (RBC) vary between a hematocrit of 21–24% (restrictive) to 27–30% (liberal). The benefit of a restrictive practice is decreased exposure to RBC transfusion by 43% across a broad range of clinical specialties. There is no evidence that mortality or morbidity is affected compared to a liberal transfusion strategy [1]. Based upon a recent meta-analysis, the current evidence does not support the notion that restrictive RBC transfusion strategies are inferior to liberal RBC strategies in patients undergoing cardiac surgery. In general, a restrictive red blood cell transfusion strategy does not have a statistically significant effect on the risk of myocardial infarction (RR 1.01, 95% CI 0.81–1.26; $I^2 = 0$), stroke (RR 0.93, 95% CI 0.68–1.27, $I^2 = 0$), renal failure (RR 0.96, 95% CI 0.76–1.20, $I^2 = 0$), or infection (RR 1.12, 95% CI 0.98–1.29, $I^2 = 0$) [2].

Define the Hemodynamic Goals

The assessment of cardiovascular state is necessary and a very crucial step in the perioperative management of each patient. More so, in the unresponsive, mechanically ventilated patient under relatively stable (as in ICU) or dynamically changing settings (as in the cardiothoracic OR). Any and all interventions, including vasoactive and cardiac medications and i.v. fluids, from crystalloids to albumin to blood and blood products, should have a clearly defined goal. In the majority of interventions for the majority of patients, the goal is always to optimize cardiac output (cardiac index) thus improving organ perfusion and outcome [3]. For fluid management, the type of monitoring device (invasive arterial, central pressure, non-invasive blood pressure, peripheral oximetry, echocardiography) will determine what is measurable and whether treatment is warranted or not.

It is important to set clear goals and decide upon management strategies. Is the caregiver responding to abnormal value of blood pressure, filling pressure, stroke volume or blood gas parameter? Considering what can be measured (independent or primary variable) and what is calculated (independent or secondary variable), there is a significant potential for many wrong assumptions. Let's consider some scenarios: (a) systemic hypotension with or without pulse pressure variability, (b) low cardiac index (CI) without taking into account the heart rate (HR) (when stroke volume [SV] is the primary variable in almost all techniques), (c) low CI and high systemic vascular resistance [SVR] (redundant and unnecessary, since the latter is a secondary parameter based on calculation of CI), (d) increased pulsed pressure variation (PPV), a dynamic index of fluid responsiveness, which depends on accurately set up of invasive arterial line monitoring system, absence of arrhythmias, etc.), (e) low central venous pressure (CVP) or a downward trend. In all scenarios, the foundation of measurements, the limitations of the method and whether it is applicable or not should be taken into account before a fluid intervention.

In the particular case, hemodynamic goals relevant to fluid management are normotension and preservation of baseline cardiac function. Autologous normovolemic hemodilution (ANH) should be considered, since a restrictive transfusion strategy is not risky and may reduce RBC and non-RBC transfusion postoperatively [4, 5]. Prior to sternotomy, baseline stroke volume should be measured with TEE and indexed to BSA (SV_i) and the PPV recorded. If PPV >13%, the patient is most likely hypovolemic. A 500 ml bolus of i.v. crystalloid solution should infused and reassess, along with re-measuring SV_i. The ideal response would be decreased PPV and increased SV_i. In this case, ANH should be practiced carefully, by maintaining normolomia and supporting myocardial perfusion pressure while avoiding tachycardia. While chest is closed, Once the chest is opened, PPV will not be valid anymore, and all fluid status decision should be made upon visual inspection of the right heart free wall, the SV_i as measured with TEE. ANH withdrawn blood should be re-transfused after heparin reversal with protamine and PPV should be considered once the chest is closed, as well as, in the ICU.

When Is i.v. Volume Expansion Indicated?

Many parameters in combination should be considered when deciding whether i.v. volume expansion is indicated. Systemic hypotension and low SV_i are two widely accepted goals.

Central Venous Pressure Is Not a Good Indicator of Hypovolemia

Intravascular expansion based upon the actual value (or trend) of CVP is wrong. It is very well known and should be an accepted fact that the relationship between CVP and blood volume is very poor and the CVP trend cannot predict the hemodynamic response to fluid challenge [6]. This is the case in either ICU or OR settings, since the area under the receiver operating characteristic curve was 0.56 (95% CI: 0.52–0.60) for ICU patients and 0.56 (95% CI: 0.54–0.58) for OR patients [7].

Dynamic Indices of Fluid Responsiveness: Pulse Pressure Variation (PPV)

Cyclic changes in airway pressure affect the filling of cardiac chambers and result in pulse pressure variation (PPV). PPV is a dynamic index of fluid responsiveness [8], and much more reliable than static parameters, such as CVP, PA occlusion pressure or LV end-diastolic volume. In a pooled analysis of 685 mechanically ventilated patients, the area under the receiver operating characteristic curve was 0.78 for PPV, 0.72 for SVV, vs 0.55 for CVP, 0.56 for LV end-diastolic volume index and 0.64 for LV end-diastolic area index. PPV is automatically calculated from invasive arterial pressure waveform by modern monitoring devices. Clinically applicable PPV values are <9% to indicate non-responders and >13% to indicate responders to volume expansion. About a quarter of mechanically ventilated patients will fall in a "gray zone" between 9% and 13%, where PPV is not reliably predictive of fluid responsiveness. In the same group of patients, CVP lacked predictive value AUC: CVP 0.57 (95% CI: 0.54–0.59) vs PPV 0.89 (95% CI: 0.86–0.92) [9]. Generally, the magnitude of PPV is related to the degree of hypovolemia; values of PPV >12–15% are considered clinically relevant and predictive of fluid responsiveness, that is, in hypotensive patients with PPV >12–15%, intravascular expansion should be the treatment of choice. However, one should keep in mind the limitations of the technique. For PPV to accurately relate to intravascular volume, the patent should be mechanically ventilated ($V_t \geq 8$ ml/kg), not have arrhythmia or extrasystoles, and have a heart rate to respiratory rate ratio > 3.6, among others. In a 1 day point-prevalence study of PPV validity criteria in 26 ICUs (>8 beds each) in 22 French hospitals, only 10 out of 311 ICU patients fulfilled all required PPV validity requirements [10]. Limitations such as those should be considered when PPV is used for fluid titration in hypotensive patients.

Validity of PPV in Cardiac and Thoracic Surgery

In a systematic review of PPV (and SVV) in open-chest settings, such as in sternotomy (cardiac surgery) or thoracotomy (thoracic surgery), a significant heterogeneity was noticed. Small sample size and differences among devices, mechanical ventilation settings, fluid challenge methodologies and end-point variables varied among studies so that PPV (and SVV) should be considered inaccurate in predicting fluid responsiveness in open-thorax settings [11]. In a recent study, SVV (and PPV) were compared before and after fluid challenge in patients undergoing elective thoracic surgery via open thoracotomy or video assisted thoracoscopy. SVV (and PPV) were not different between responders (increase in $SV_i \geq 10\%$) and non-responders and regardless of surgical approach. All together, SVV (and PPV) cannot be the sole parameters, particularly if patients are not hypotensive, i.e., there is no clinical indication for intervention, to guide fluid administration in open chest settings [12].

Systolic Pressure Variation

The decrease in systolic pressure in response to a standardized maneuver consisted of three consecutive mechanical breaths with inspiratory pressures of 10, 20 and 30 cmH_2O is used to generate a slope (respiratory systolic variation test). The area under the receiver operating curve was 0.96 (95% CI: 0.92–1.0) for this slope and 0.95 (95% CI: 0.89–1.0) for PPV, with threshold values of >0.51 $mmHg/cmH_2O$ and > 9.4%, respectively to detect fluid responsiveness (increase in SV >15%). The SPV had similar clinically actionable values: ROC 0.92 (95% CI: 0.85–0.99) and threshold >8.5 mmHg. All patients were studied with closed chest and in pressure control mechanical ventilation [13]. The respiratory systolic variation can be automatically calculated in Draeger OR ventilators. Following major surgery, it was useful to predict fluid responsiveness if its angle was >20° [14].

Esophageal Doppler

Esophageal Doppler measures the velocity of the descending aorta blood flow. The integral of the velocity is used to derive a SV calculation based upon nomograms. Respiration-induced variation of SV >15–18% measured by esophageal Doppler predicted fluid responsiveness in anesthetized and/or ICU patients [15, 16].

Plethysmographic Variation (PVI)

The amplitude of the oximetry plethysmographic variation may be considered a surrogate of SV; it can be automatically calculated by commercial devices as a plethysmographic variability index. In anesthetized patients under volume controlled mechanical ventilation, baseline PVI was less reliable than PPV and SVV for predicting fluid responsiveness in patients receiving i.v. norepinephrine [17].

Echocardiographic Indices

In CT surgery, intra- and post-operative echocardiography is gaining a monitoring role over traditional devices, such as CVP and PAC. An easily obtained

parameter is the velocity of blood at fixed orifices, such as the left ventricular outflow tract or the aortic valve. Since the orifice cross-area is considered constant, the velocity time integral (VTI) is reflective of stroke volume (this is the foundation of esophageal Doppler). In an experimental setting, the aortic VTI was found to progressively decrease and its respiratory variation to increase proportionally to controlled bleeding. The respiratory variation of aortic VTI was found to be strongly related to fluid replenishment. The static measurements of LV diameter did not relate to fluid responsiveness [18]. This was translated to a human study, when a100 ml colloid was i.v. infused over 1 min and the LV outflow tract VTI was measured with TTE in intubated, mechanically ventilated ICU patients. This "mini challenge" maneuver, showed that respiratory variation of LV outflow tract VTI ≥10% was predictive of fluid responsiveness with an area of the receiver operating characteristic of 0.92 (95% CI: 0.78–0.98). PPV and CVP were less predictive, with area of the receiver operating characteristic of 0.55 (95% CI: 0.74–0.98) and 0.61 (95% CI: 0.41–0.79) [19]. This is particularly important in the postoperative cardiothoracic ICU, where fluid overload is the norm.

Should i.v. Fluids Administered if Patients Are Found to Be Fluid Responsive?

The short answer is no! Fluid responsiveness should not be the goal. Fluid responsiveness is simply a measurement (by different methods/devices, such as PPV, SVV, SPV, PVI), it requires that the patient is mechanically ventilated (with $V_t > 8$ ml/kg; not always the current clinical practice), has a closed chest cavity (so that cyclic airway pressures effect cardiac filling; not the case in sternotomy or thoracotomy), with a not fast heart rate or arrythmias, in order to be accurate. Its utility varies. For example, a meta-analysis showed that PPV is not as good predictor of fluid responsiveness compared to CO (and SV) if passive leg raising is the provocative maneuver [20]. If the anesthetized patent is hypotensive and monitored with standard, non-invasive monitors, PVI if available may be used to detect whether fluid responsiveness is present, and first treatment option should be intravascular volume expansion. If an arterial line is present, PPV (or SPV) should be used. If blood pressure or other "goal" are within normal range, no volume expansion should be attempted.

What Is the Preferred Intravascular Volume Expander?

In cardiac surgery, there is a definitive change and crystalloids are preferred over colloids (starches, gelatins or albumin) as shown in a recent European survey [21] (Fig. 26.1).

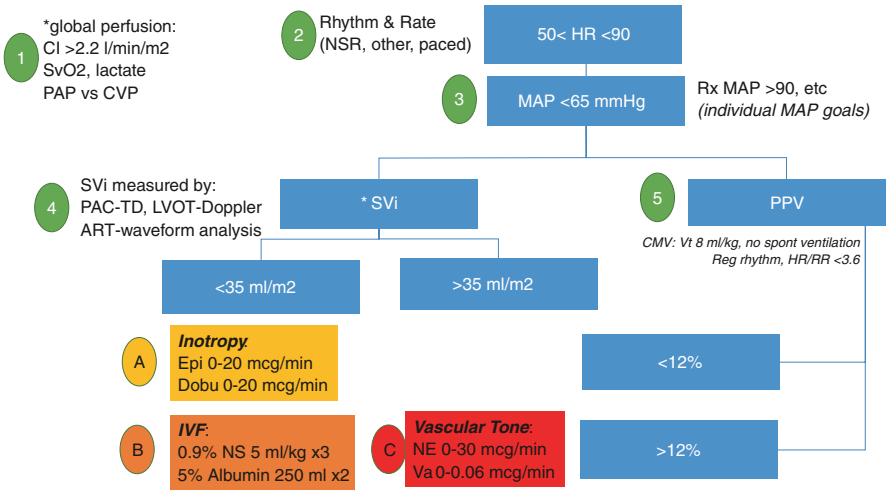

Fig. 26.1 Pragmatic, goal-directed hemodynamic management. (1) a global perfusion "target" is chosen. This will vary, depending upon the invasiveness (or not) of the monitoring. It can be cardiac index (CI), mixed venous oxygen saturation (SvO2), pulmonary artery or central venous pressures. (2) Heart rate and rhythm are important to consider and correct accordingly. (3) Blood pressure (mean arterial pressure [MAP]) should be kept with individualized "normal" range. (4) Indexed stroke volume (SVi) should be measured via thermodilution (pulmonary artery catheter [PAC]), Doppler echocardiography (left ventricular outflow tract velocity and orifice) or invasive arterial line (ART) waveform analysis. (5) Alternatively, the pulse pressure variation (PPV) can be measured from an arterial line waveform (or its surrogate, plethysmographic variation index from peripheral oximetry signal). PPV requires controlled mechanical ventilation, regular rhythm and relatively shower heart rates. The decision tree can be simplified to: (**a**) low SVi without fluid responsiveness (PPV <12%), indicating inotropic support, (**b**) low SVi with fluid responsiveness (PPV >12%), indicating hypovolemia, (**b**) normal SVi with increased fluid responsiveness, indicating increase in vascular tone

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Case Scenario of Fluid Management for Thoracic Surgery

27

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Abstract

Perioperative fluid management for thoracic surgery is challenging and a subject of debate. Acute lung injury is not uncommon, and a major cause of morbidity and mortality after lung resections and esophagectomy. Its pathogenesis is multifactorial and excessive perioperative fluid administration is considered a contributing factor. Restrictive and goal directed fluid therapy are described for thoracic surgery and it seems beneficial when applied with protective lung ventilation.

Key Points

- Fluid management in thoracic surgery is unique and a subject of debate.
- Acute lung injury is a major concern after pneumonectomy, less extensive lung resections and esophagectomies.
- The etiology of acute lung injury after thoracic surgery is multifactorial and excessive intravenous fluid administration perioperatively considered a contributing factor.
- The recommended strategy of fluid management in thoracic surgery is either restrictive or goal directed coupled with protective lung ventilation.
- The risk of fluid overload and tissue edema should be balanced against the risk of hypoperfusion and end-organ ischemia.

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Introduction

Perioperative fluid management is a corner stone in the anesthetic management. One of the most difficult tasks in the clinical practice is to accurately predict the intravascular volume. Patient's skin turgor, blood pressure, pulse rate and urine output are not accurate in reflecting the intravascular volume. Central venous pressure and Pulmonary artery occlusion pressure are indirect indicators of filling volume and poorly predict the hemodynamic response to fluid challenge. The use of echocardiographic indices as inferior vena cava diameter, left ventricular end-diastolic area index (LVEDAI), transesophageal Doppler; or global end-diastolic volume index determined by transpulmonary thermodilution are not feasible in every case. Over the last two decades, dynamic indices as systolic pressure variation (SPV), pulse pressure variation (PPV) and stroke volume variation (SVV) utilizing the heart lung interaction have been used to predict volume responsiveness.

Fluid management in thoracic surgery is unique and a subject of debate. The negative effect of volume overload on the lungs is a major concern as well as the negative effects of tissue hypoperfusion and end-organ ischemia with hypovolemia. During pneumonectomy, fluid infusion of more than 2 l was found to be a risk factor to develop acute lung injury (ALI), and perioperative fluid infusion of more than 2.5 l has a negative effect on postoperative mortality. Similar findings were noticed in less extensive lung resections. In esophagectomy, intraoperative fluid administration of more than 5 liters was associated with acute lung injury.

Acute lung injury is a major cause of mortality and morbidity after lung resection and esophagectomy with excessive fluid administration suggested to be a risk factor.

During thoracic anesthesia, a balance should be achieved between fluid administration, vasoactive/inotropic therapy to optimize cardiac output and oxygen delivery to the tissues on one side and avoiding fluid overload and acute lung injury on the other side. The risk of fluid overload and tissue edema should be balanced against the risk of hypoperfusion and end-organ ischemia.

The classic approach of fluid replacement and maintenance during anesthesia should definitely be revisited and restructured in the case of thoracic surgery. A superior approach would be the adoption of restrictive fluid versus goal directed strategy maintaining normovolemia with a better understanding of the concept of endothelial glycocalyx together with the application of protective lung ventilation.

Case Scenario

61 years old female, 79 kg, who is a former smoker (10 pack years), initially presented to the emergency department for shortness of breath. CT imaging revealed right pleural effusion, right upper lobe opacity with collapsed right middle and right lower lobes, and mediastinal shift to right. Bronchoscopy visualized a right main stem mass occluding 90% of the right main bronchus and was debulked. Cytology confirmed poorly differentiated non-small cell carcinoma from the right mainstem mass. Pulmonary function tests reported FEV1 1.51L/61% and DLCO of 49% of predicted. Trans-thoracic echocardiography showed normal biventricular function and no significant valve lesions.

Patient presented to the operating room for right pneumonectomy. Standard ASA monitors applied, 16 G peripheral intravenous catheter and left radial 20G arterial catheter were inserted. Patient received 3 mg of midazolam before placement of T5/6 epidural catheter and level of anesthesia achieved was T4. Uneventful induction of general anesthesia using fentanyl, propofol and rocuronium, single lumen endotracheal tube was placed first for bronchoscopy then switched to 37 left double lumen tube (for lung isolation) followed by placement right internal jugular central venous catheter(for volume resuscitation and vasoactive medications if needed).

Maintenance of general anesthesia was achieved by sevoflurane, rocuronium and epidural infusion started for intraoperative and later postoperative analgesia. The case proceeded through right thoracotomy.

Discussion

Excessive fluid administration during thoracic surgery has been shown consistently to be a risk factor to develop lung injury. On the other hand, too aggressive fluid restriction can compromise vital organs perfusion.

Pulmonary edema has been identified as a complication after pneumonectomy, usually develops on 1-fourth day postoperatively [1], this has been observed as well in less extensive lung resection and esophagectomy [2–4].

During Pneumonectomy, fluid infusion of more than 2 l was found to be a risk factor to develop acute lung injury (ALI) [5–7],and perioperative fluid infusion of more than 2.5 l has a negative effect on postoperative mortality [8].Similar findings were noticed in less extensive lung resections [9, 10].

In esophagectomy, intraoperative fluid administration of more than 5 l was associated with acute lung injury [4].

Acute lung injury is a major cause of mortality and morbidity after lung resection [11].The incidence of acute lung injury after lung resection is between 2–4% [10, 12, 13], with mortality rate around 40% [11].

The incidence of acute respiratory distress syndrome (ARDS) after esophagectomy was found to be 16% and 14.5% with associated mortality rate of 14% and 50% respectively in two studies. With excessive fluid administration suggested to be a risk factor in both studies [4, 14].

The findings in this acute lung injury resemble the features of non-cardiogenic pulmonary edema, acute respiratory distress syndrome (ARDS) [15]. Definitions of ARDS and ALI are shown in (Table 27.1) [16] while ARDS severity classification is shown in (Table 27.2) [17].

Pathogenesis of ALI

For decades, the fundamental principle by Starling described the fluid shift between the intravascular and interstitial spaces. It explains fluid filtration at the arteriolar end of the capillaries into the interstitium and its absorption at the venule end [18].

Table 27.1 ARDS and ALI definitions [16]

ARDS and ALI definitions per the American Consensus conference diagnostic criteria for ARDS& ALI
– Acute onset
– Bilateral infiltrates on chest radiograph consistent with pulmonary edema
– Hypoxemia
– ALI: $PaO_2/$fraction of inspired $O_2(FiO_2)$ <300
– ARDS: PaO_2/FiO_2 < 200
– Absence of heart failure
– No clinical evidence of left atrial hypertension
– Pulmonary artery occlusion pressure < 18 mmHg

Table 27.2 Acute lung injury Berlin criteria [17]

ARDS severity	PaO_2/FiO_2	Associated mortality
Mild	200–300	27%
Moderate	100–200	32%
Severe	<100	46%

There is evidence that only filtration takes place into the interstitium and there is no reabsorption at the venule end [19], suggesting the importance of the lymphatic system in maintaining the interstitial fluid volume. For this reason, Starling principle is revisited with the proposal of the glycocalyx model to describe the fluid shift more accurately. The endothelial glycocalyx is described in details in other parts of this book.

Briefly the endothelial glycocalyx layer is at the luminal surface of vascular endothelium that is involved in fluid homeostasis and regulation. It is formed predominantly of proteoglycans, mainly syndecan-1, and covalently bounds glycosaminoglycans, mainly heparan sulfate. Together with bound plasma proteins, hyaluronan, and solubilized glycosaminoglycans, the endothelial glycocalyx forms the endothelial surface layer (ESL), the physiological active form.

The ESL plays a major role in vascular homeostasis, regulation of filtration processes along the vessel wall, and protection from adhesion of leukocytes and platelets to the endothelial cells.

EGL is a fragile structure that can be disrupted by inflammation and release of cytokines [20, 21], surgical trauma, ischemia-reperfusion injury and hypervolemia (hypervolemia damages the EGL via dilution of plasma proteins and by the release of atrial natriuretic peptide that strips the EGL) [22–25] increasing the endothelial permeability and probably results in ALI. Interventions that could protect against EGL disruption are shown in (Table 27.3) [26–37].

A Multi-hit Hypothesis for ALI [38]

A multi-hit hypothesis is a proposed mechanism for developing ALI. Surgical trauma primes the lungs by activation of a systemic inflammatory response. These lungs become more susceptible to subsequent insults [39] like lymphatics damage [40],

alveolar overdistension [7], oxygen toxicity [41], or FFP administration [42]. It is not only fluid overload that causes ALI after thoracic surgery, definitely it is a contributing factor but together with other factors as lymphatics damage and pulmonary endothelial damage. Postoperative acute lung injury risk factors are shown in (Table 27.4) [7, 11, 13, 42–48].

Table 27.3 Studied interventions linked to protection against EGL disruption [26–37]

Hydrocortisone Antithrombin	Protect against degradation initiated by TNF-α in ischemic-reperfusion injury and inflammation
Protein C	Prevented capillary perfusion deficit in endotoxemia
Nitric Oxide	Protective when administered during reperfusion
Hyaluronic acid and chondroitin sulphate	Both together partially regenerate the capillary glycocalyx damaged by hyaluronidase
Albumin Hydroxyethyl starch	Decrease fluid extravasation in ischemia/reperfusion glycocalyx damage
Metformin	Improve the barrier properties of the glycocalyx in non-insulin dependent diabetic animal studies
Sulodexide	Enhance glycoseaminoglycan synthesis

Table 27.4 Factors contributing to postoperative acute lung injury [7, 11, 13, 42–48]

Factors contributing to postoperative lung injury	
Surgical factors	
• Right pneumonectomy more than left pneumonectomy	More lung tissue is resected > 90%of lymphatic drainage of the right lung is ipsilateral and > 50% of the left lung lymphatic drainage is through right sided lymphatics [43].
Patient related risk factors [11, 13, 42, 44–47] • Advanced age • Low body mass index • ASA physical status • Diabetes • Smoking • COPD • Alcohol abuse • Preoperative albumin level • Predicted postoperative lung perfusion <55%of preoperative value • Predicted postoperative FEV1 < 45% • Reoperation • Blood loss • Pulmonary metastasis	
Intraoperative Factors ▪ Intravenous fluid management ▪ Mechanical ventilation strategy [7, 48]	

Case Scenario Continued

Surgery lasted 5 hours under protective single lung ventilation strategy; tidal volume 4 ml/kg IDW, Peak inspiratory pressure < 30 cmH_2O, plateau pressure < 20 cmH_2O, PEEP of 5 and FIO_2 the lowest to maintain $SpO_2 > 90\%$.

Patient received crystalloid maintenance fluid of lactated ringer 2 ml/kg/h, estimated blood loss was 700 ml for which she received 500 ml of albumin 5% and 200 ml of cell salvage blood, urine output total of 170 ml during the case.

Norepinephrine infusion was titrated to keep the mean arterial pressure (MAP) within 20% of the patient's baseline.

Intraoperative Fluid Management Strategy During Thoracic Surgery

Anesthesiologists traditionally replace the postulated fluid deficit based on preoperative fasting, insensible losses that results from perspiration and tissue exposure during surgery in addition to third-space fluid shift. These assumptions proved to be inaccurate and grossly overestimated [49–51]. In fact, fasting does not decrease the intravascular volume [49].

Third space is not the interstitial space but a hypothetical compartment that is not involved in the fluid exchange between the intravascular and the interstitial space. Its location is not clearly identified but speculated to be the traumatized tissue and the gastrointestinal tract. The evidence is weak to support the existence of this third space [52].

Pursuing this assumed fluid deficit will only result in fluid overload where most of this intravenously administered fluid will shift from the intravascular to the extravascular compartment during and after the surgical procedure.

Nature of the Fluid to Use Perioperatively; Colloids or Crystalloids

Crystalloids can further be classified into hypertonic, hypotonic (like dextrose 5% in water and 0.45% NaCl infrequently used intraoperatively), and isotonic fluids.

Isotonic solutions represented by 0.9% saline (normal saline) remains the most commonly used intravenous solution in the world.

The choice of saline 0.9% is debated by many because the high concentrations of sodium and chloride (154 mmol/l) resulting in salt overload and hyperchloremic acidosis in volumes more than 2 l and has been linked to changes in renal function in healthy volunteers, increase incidence of blood transfusions and mortality in patients undergoing abdominal surgery [53–55].

Lactated ringer and plasmalyte (acetate-buffered solution) are called balanced solutions, they are closest to the physiological norm, but still not identical to plasma. They are more suitable as maintenance fluids. In contrast to normal saline, balanced crystalloids contain anions that can be metabolized, such as lactate or acetate, which

maintain electrolyte neutrality and are less associated to metabolic acidosis, albeit they are metabolized to bicarbonate [56, 57].

Multiple colloid fluids are commercially available; the most commonly used are; human albumin solution, hydroxyethyl starch, and succinylated gelatins. Hydoxyethyl starch is associated with coagulopathy, and kidney injury requiring renal replacement therapy, which may lead to a higher mortality rate in sepsis and critically ill patients [58].

Colloids due to the greater volume expansion per unit infused and maintenance of Colloid Osmotic Pressure (COP) compared to crystalloids are more suitable for replacement of blood loss when blood transfusion is not indicated.

Restrictive and Goal-Directed Fluid Therapy

Restrictive Fluid Management

It is not only excessive fluid administration that can be detrimental but aggressive fluid restriction that results in lower cardiac output and impair tissue perfusion. At the present time there is no unifying definition of what is restrictive and what is liberal.

Restrictive fluid strategy is possible by limiting the crystalloid maintenance fluid to 1–2 mL/Kg/hr. and replacing any significant blood loss with colloids 1:1 volume, maintaining cardiac output and normovolemia with the judicious use of vasopressors/inotropes.

The main concern of fluid restriction is tissue hypoperfuion with specific emphasis on kidney hypoperfusion that can result in acute kidney injury (AKI).

When patients develop AKI, there is prolonged hospital stay, [59] increased cardiopulmonary complications [59, 60], and mortality [60].

Risk factors to develop AKI are; American society of anesthesiologists class(ASA) 3 and 4, forced expiratory volume in 1 second, the use vasopressors (although it is not clear is it the use of vasopressors or the underlying hypotension, uncompensated hypovolemia or patient/procedure related comorbidities), duration of the anesthetic [60], hypertension, peripheral vascular disease, pre-existing renal dysfunction, preoperative use of angiotensin II receptor blockers, intraoperative use of colloids(high molecular weight older generation of hydroxyethyl starch was associated with AKI in a dose dependent manner) and open procedures [59].

The incidence of AKI after lung resection is around 6% but only 0.1% require renal replacement therapy [59, 60].

The development of Acute Kidney Injury Network (AKIN) and Risk, Injury, Failure, Loss of kidney function, End-stage Kidney disease (RIFLE) classifications provides guidance to rank the severity of renal injury in the perioperative period (Tables 27.5, 27.6) [61, 62].

Hypovolemia and prolonged hypotension with reduced perfusion of the kidneys are not the only causes of intraoperative oliguria, but non-renal causes such as the release of anti-diuretic hormone (ADH) in response to surgery can also cause oliguria.

Table 27.5 Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease (RIFLE) classification [61]

Class	Glomerular filtration rate (GFR)	Urine output
Risk	↑Serum creatinine (SCr) × 1.5 or ↓ GFR >25%	<0.5 mL/kg/h × 6 h
Injury	↑ SCr × 2 or ↓ GFR >50%	<0.5 mL/kg/h × 12 h
Failure	↑ SCr × 3 or ↓ GFR >75% or if baseline SCr ≥353.6 μmol/L (≥4 mg/dL) ↑ SCr >44.2 μmol/L (>0.5 mg/dL)	<0.3 mL/kg/h × 24 h or anuria × 12 h
Loss of kidney function	Complete loss of kidney function >4 weeks	
End-stage kidney disease	Complete loss of kidney function >3 months	

Table 27.6 Acute kidney injury network (AKIN) network criteria [62]

Stage	Serum creatinine (SCr)	Urine output
1	↑ SCr ≥26.5 μmol/L (≥0.3 mg/dL) or ↑SCr ≥150 a 200% (1.5–2×)	<0.5 mL/kg/h (>6 h)
2	↑ SCr >200 a 300% (>2–3×)	<0.5 mL/kg/h (>12 h)
3	↑ SCr >300% (>3×) or if baseline SCr ≥353.6 μmol/L (≥4 mg/dL) ↑SCr ≥44.2 μmol/L (≥0.5 mg/dL)	<0.3 mL/kg/h (24 h) or anuria (12 h)

Based on the available evidence, it does not seem that restrictive fluid strategy is associated with increase in the incidence of AKI [63, 64].

Goal-Directed Fluid Therapy in Thoracic Surgery

There is a growing evidence supporting the importance of goal directed fluid therapy and hemodynamics management in non-thoracic surgery. It showed lower incidence of postoperative AKI, pneumonia, intensive care and hospital stay. It is intended to maintain tissue perfusion and avoid intraoperative and postoperative complications with fluid therapy guided by esophageal Doppler monitoring (TDM), and dynamic hemodynamic parameters that predict fluid responsiveness as stroke volume and pulse pressure variations (SVV and PPV respectively) together with the judicious use of vasopressors (e.g. phenylephrine, ephedrine, norepinephrine) and inotropes (e.g. dobutmaine and epinephrine) to optimize the mean arterial pressure and cardiac index.

TDM produces a flow velocity profile for each heartbeat by analyzing the blood flow in the descending aorta. It produces a waveform that can be used in a non-invasive measurement of the stroke volume by utilizing normogram of biometric data. When used in thoracic surgeries, TDM can detect and correct low flow conditions and guide fluid management.

Patients should only receive a fluid bolus if they are preload responsive and likely to benefit from the fluid bolus, and the potential benefits and risk should be

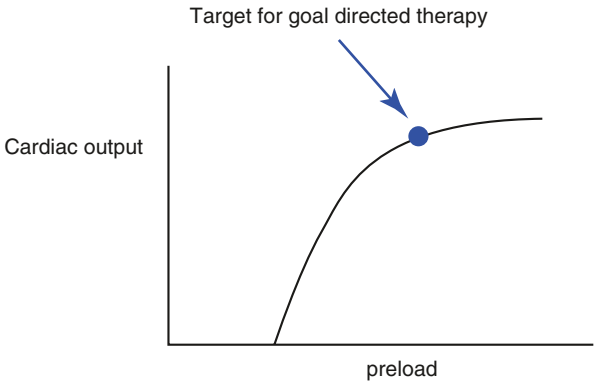

Fig. 27.1 Target for goal directed therapy

evaluated prior to each fluid bolus. The target for goal directed therapy is shown in (Fig. 27.1).

Below is an example of goal-directed hemodynamic algorithm to guide intraoperative fluid therapy and the use of vasopressor and inotropic therapy in the goal-directed therapy utilizing transesophageal Doppler. Step A takes place after induction of anesthesia (Fig. 27.2).

Frank–Starling and extra-vascular lung water (EVLW) curves show that with less fluid responsiveness, there is significant increase in EVLW and tissue edema (Fig. 27.3).

EVLW was shown to be an independent predictor of survival in critically ill patients [65].

The principle of the functional parameters of preload (SVV, PPV) is based on the mechanical ventilation cyclic increase in the intrathoracic pressure. This change has a variable effect on the ventricular loading and depends on the patient's volume status.

A pulse pressure variation (PPV) or stroke volume variation (SVV) of >13% was shown to be predictive of fluid responsiveness [66, 67].

The predictive value of these parameters showed mixed result in thoracic surgery. It relies on the tidal volume used, PPV predicted fluid responsiveness with protective one lung ventilation (OLV) but not with non-protective lung ventilation in thoracotomy [68].

Others reported the ability of SVV in predicting fluid responsiveness in OLV if the tidal volume is at least 8 mL/kg [69].

Furthermore, there is a controversy on the fluid responsiveness predictive value of SVV in open thoracotomies; SVV guided fluid management was not validated in thoracic surgeries under OLV after the institution of open thoracotomy. However, this did not result in pulmonary fluid overload [70].

Protective lung ventilation should be instituted with either Restrictive or goal-directed fluid management in thoracic surgery. Protective ventilation approach includes pressure-controlled ventilation with low tidal volumes, restriction of inspired oxygen concentrations, limitation of inspiratory pressure, use of repetitive alveolar recruitment maneuvers and PEEP.

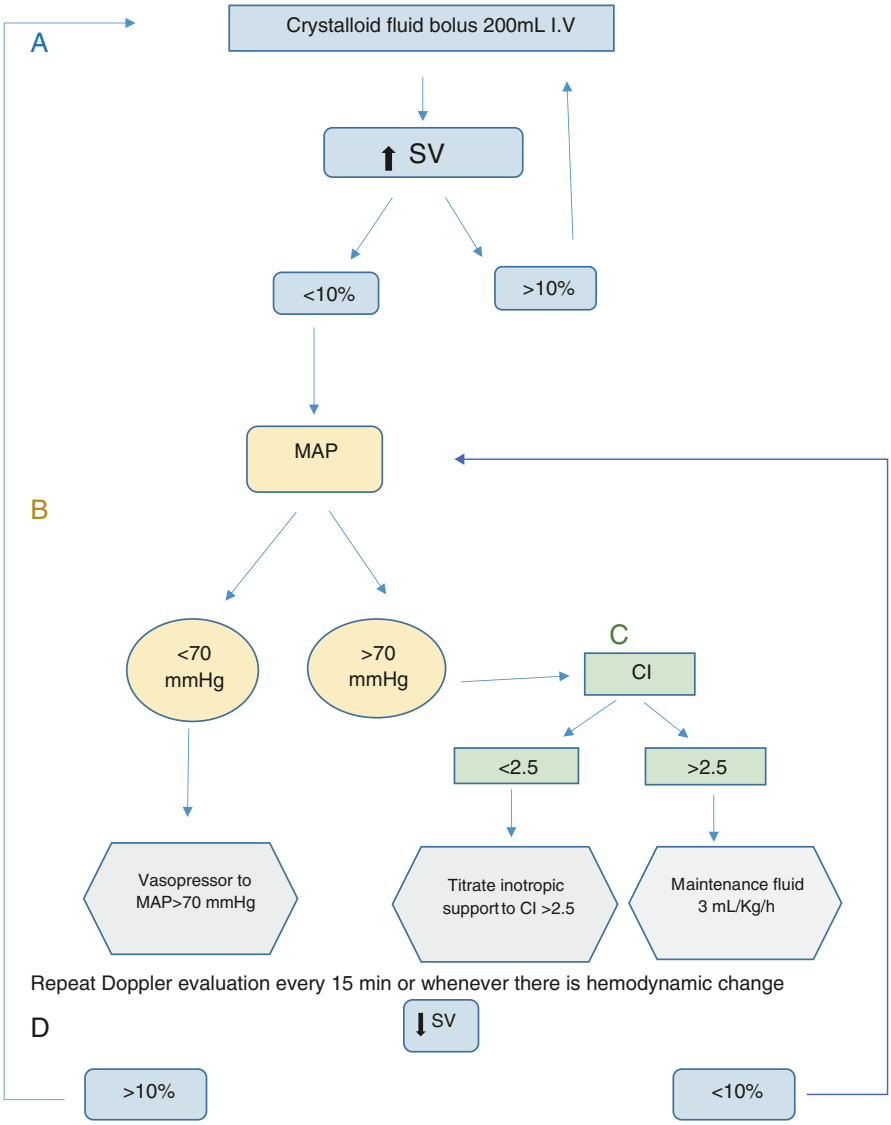

Fig. 27.2 Example of goal directed therapy utilizing TDM in thoracic surgery. SV stroke volume, MAP mean arterial pressure, CI Cardiac Index l/min/m^2. Adapted from Kaufmann, K.B. et al. Oesophageal Doppler guided goal-directed haemodynamic therapy in thoracic surgery—a single centre randomized parallel-arm trial. British Journal of Anaesthesia, Volume 118, Issue 6, 852–861. Feldheiser A, Conroy P, Bonomo T et al. Development and feasibility study of an algorithm for intraoperative goal directed haemodynamic management in noncardiac surgery. J Int Med Res. 2012;40:1227–1241

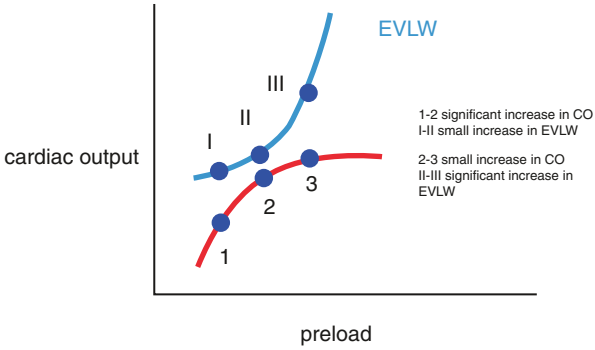

Fig. 27.3 Frank-Starling and extra-vascular lung water curves. Adapted from P. E. Marik, J. Lemson, Fluid responsiveness: an evolution of our understanding. BJA: British Journal of Anaesthesia, Volume 112, Issue 4, April 2014, Pages 617–620

Case Scenario Continued

Patient was transferred to the intensive care unit, extubated the same day of surgery. The first postoperative day the patient's fluid balance was positive 450 ml, she resumed oral intake the next day and was discharged to regular nursing floor after 2 days in the intensive care unit.

Her SpO_2 was maintained >94% on nasal O_2.

The patient's chest x-ray on postoperative day (POD) 4 showed mild hazy reticular changes in the left lung, suggesting interstitial edema or inflammatory change, no overt consolidation, effusion, or pneumothorax, and diffuse opacification of the right hemithorax associated with right pneumonectomy history. On Postoperative day 7 the chest x-ray showed Stable complete opacification of the right hemithorax linear density at the left lung base, likely subsegmental atelectasis or scar, no new consolidative opacity and no pneumothorax.

Postoperative serum creatinine (S.Cr.) and Blood Urea Nitrogen (BUN)

	Preoperative	POD1	POD3	POD7
S.Cr.	0.55	0.54	0.56	0.63
BUN	13	9	19	11

Patient continued to improve and finished her chemotherapy 5 months after surgery.

Interventions that are possibly beneficial to avoid postoperative ALI after thoracic surgery are shown in (Table 27.7) [71–73].

Table 27.7 Suggestions to avoid postoperative ALI [71–73]

Anesthetic and Perioperative fluid management suggestions to avoid postoperative ALI after thoracic surgery
• Unrestricted clear liquid (carbohydrate based) to 2 hours before surgery.
• Third space does not exist in thoracic surgery.
• Fluid administration intraoperatively and in the first 24 hours < or equal 2 mL/kg/h.
• Perioperative fluid balance < or equal 1.5 L of positive balance.
• Vasopressors or inotropes as needed to correct tissue hypoperfusion or anesthesia-induced vasodilatation.
• Not to pursue urine output >0.5 ml/kg/h.
• Application of protective lung ventilation.
• Use of inhalational anesthetics (Sevoflurane) preferred to total intravenous anesthesia.
• Early termination of intravenous fluids and resumption of oral fluids when appropriate.

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Fluid Management During Major Vascular Surgery

28

James R. Rowbottom

Abstract

Major vascular surgery presents complex and critical challenges to perioperative fluid management. There are increased risks of morbidity and mortality. These risks can be influenced by many factors including patient comorbid conditions, acute blood loss, application and removal of an aortic cross-clamp, as well as choice of fluid for administration. Patients typically are medically complex and although often preoperatively optimized, their comorbidities continue to put them at an increased risk. A thoughtful approach is necessary to assure appropriate resuscitation in order to avoid complications.

Key Points

1. Vascular surgery patients are medically complex and are not always in optimal condition.
2. AAA surgery is a physiologically demanding procedure with significant cardiovascular demands.
3. Other non-cardiac organ systems are challenged with AAA surgery.
4. New monitoring paradigms are evolving which will change care of these patients in the future.
5. Restrictive fluid management appears advantageous over liberal fluid approaches.

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Introduction

The number of major vascular procedures is increasing with the aging population. The prevalence of aortic aneurysm is 4.5–7.7% with a mortality rate of 4–10% for open abdominal aortic aneurysm repairs [1, 2]. Care of the patient undergoing aortic aneurysm surgery is complex. It involves a high risk surgical procedure performed on a patient with multiple medical comorbidities. Vascular surgery patients are at increased risk for significant cardiac morbidity and mortality due to myocardial stress and increased demand, pulmonary complications, and renal complications. Acute kidney injury arises in approximately 7% of patients undergoing aneurysmectomy with normal preoperative renal function. Of those who develop renal dysfunction, mortality is increased compared with those who do not develop dysfunction [3]. Fluid shifts are common and are related to the length of surgical procedure, blood loss, insensible losses, vasodilation, and anesthetics. In this case report, we will highlight salient parts of preoperative evaluation, hemodynamic monitoring, renal protection and the impact of the aortic cross-clamp on fluid management in this patient population.

Case

A 90 kilogram 73 year old male with a past medical history of coronary artery disease, remote myocardial infarction without current symptoms, chronic renal insufficiency (serum creatinine 1.6 mg/dl), type II diabetes mellitus, hypertension, and a 50 pack year smoking history with chronic obstructive pulmonary disease presented to the emergency department with abdominal pain and nausea. He works as a custodian. His exercise tolerance is adequate and he is not significantly limited by his COPD. He does not use home oxygen. He has renal insufficiency with an elevated creatinine but no symptoms. His physical exam revealed blood pressure of 175/68 mmHg, pulse of 98 beats per minute, respirations 14 breaths per minute and a pulse oximeter reading of 97% on room air. He had clear breath sounds without wheezing and a regular rhythm with normal heart sounds. His abdomen was soft with right lower quadrant tenderness and a palpable pulsating mass. There was no rebound or guarding on palpation. He had distal pulses. His lab work revealed a WBC of $8 \times 10^3/\mu L$, hemoglobin of 10 g/dl, creatinine 1.67 mg/dL, normal amylase and lipase. Computer assisted tomography (CAT) scan revealed a large 10 cm × 9 cm infrarenal aorta-right common iliac artery aneurysm without evident leak. He was evaluated by a vascular surgeon who decided to take him to the OR emergently to do an open repair out of concern for the ongoing pain, presence of a large aneurysm and the location of the aneurysm.

Preoperative Evaluation

Ideally, this case would be completed in an elective manner to minimize the perioperative risk, but that is not appropriate in this scenario. However, a typical elective approach would include the following components:

The preoperative evaluation of a cardiac patient undergoing non-cardiac surgery has been written about extensively [4–7]. The evaluation starts with a complete history and physical exam with focus on cardiac symptoms since coronary artery disease is prevalent in the vascular surgery patient [8, 9]. A risk stratification tool is often employed to detect the level of cardiac risk associated with the surgical procedure and to assist in potentially avoiding perioperative complications. The most common risk stratification tools are the Lee Index or Revised Cardiac Risk Index (RCRI), American College of Surgeons National Surgical Quality Improvement Program (NSQIP), Gupta Myocardial Infarction or Cardiac Arrest (MICA) risk calculator and the Vascular Surgery Group of New England Cardiac Risk Index (VSG-CRI). These tools assign a percentage of risk for a cardiac complication at the time of the non-cardiac surgery. The RCRI is the most common one used. The RCRI is based on six equally weighted indices: high risk surgery, history of coronary artery disease, history of heart failure, history of cerebrovascular disease, insulin-dependent diabetes mellitus and preoperative renal insufficiency (creatinine >2 mg/dl). It has been shown to be a poor predictor in vascular surgery patients, but is still used due to simplicity and significant external validation [10]. Functional capacity, expressed in terms of metabolic equivalent of task (MET), is used as a means to judge exercise tolerance and cardiac risk perioperatively. The ability to achieve ≥4 METs of activity without symptoms is a positive prognostic indicator. The Duke Activity Status Index (DASI) is one of the most commonly used indicators for activity and METs [11]. Other areas explored include evaluation for evidence of heart failure, valvular heart disease, arrhythmias, presence of a cardiac implantable electronic device, and coronary artery disease. There is limited use of cardiac stress testing and cardiac catheterization as an evaluation tool unless it would be indicated independent of the surgical procedure. Newer biomarkers are being studied and used to evaluate for cardiac risk including troponin, B-type natriuretic peptide (BNP) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP). These biomarkers may indicate a patient at high risk of a cardiac event if they are elevated preoperatively [12]. An electrocardiogram (ECG) is usually done on the basis of RCRI since the patient is undergoing a high risk procedure. It serves several purposes including identification of rhythm, abnormal conduction, Q waves and ST—T wave abnormalities, as well as to serve as a baseline for post-operative comparison should there be any intraoperative or postoperative cardiac issues. Although commonly ordered, a preoperative echocardiogram (ECHO) is not always necessary. The ECHO is useful in determining ejection fraction, wall motion, and valvular abnormalities which can assist with perioperative hemodynamic management and serve as a baseline for post-operative care.

The highest pulmonary risk non-cardiothoracic surgery is open abdominal aortic aneurysm, therefore pulmonary risk stratification is also potentially undertaken at the preoperative interview. The pulmonary risk factors for post-operative pulmonary complications include age, asthma, chronic obstructive pulmonary disease, smoking, pulmonary hypertension, interstitial lung disease, obstructive sleep apnea, emergency surgery, duration of anesthesia, presence of congestive heart failure, altered mental status and type of surgery. Pulmonary function tests and a chest x-ray are not typically predictive of post-operative pulmonary complications unless

undergoing thoracic surgery. Not infrequently, preoperative optimization of pulmonary diseases is not undertaken since there few significant interventions except aggressive bronchopulmonary hygiene, mobilization, smoking cessation if time permits and lung expansion maneuvers [13].

A measurement of serum electrolytes and creatinine is useful in understanding the risk of post-operative renal dysfunction and potential need for renal replacement therapy. The patient will also have had a contrast CAT scan preoperatively which may insult the kidneys before beginning the procedure.

Interestingly, there is evidence that a six week period of supervised exercise preoperatively in elective AAA repair leads to decreased cardiac complications, respiratory complications, renal complications and hospital length of stay [14].

Our patient has a significant past medical history but little time for evaluation. A cardiac evaluation would be useful as this is a source of major morbidity and mortality [8, 9]. Further evaluation revealed ECG from 3 months prior. It is significant for sinus rhythm, heart rate of 80 bpm, no acute changes but evidence of a prior inferior myocardial infarction (which is identical to the one done in the emergency department on this admission), recent (2 years ago) ECHO with an ejection fraction of 55%, normal wall motion and valves. He has been NPO except for some clear fluids with medication 2 hours prior to admission (Table 28.1).

Table 28.1 Patient Medical History and Current State

Summary	
Neurologic	Intact with no deficits
Pulmonary	COPD – Continued to smoke up to time of presentation – 50 pack year smoking history – No PFT's, no home oxygen
Cardiac	Hypertension – on Amylodipine Coronary artery disease – Normal ECHO – No acute changes on EKG, old inferior MI – Beta blocker - Metoprolol
Renal	Baseline Creatinine 1.6 mg/dl – Currently at baseline
Hematologic	Normal hemoglobin and hematocrit Normal platelets and coagulation profile
Endocrine	Diabetes mellitus – Blood sugar 195 mg/dl – Oral hypoglycemic—Metformin

Anesthetic Plan

A general anesthetic with oral endotracheal tube, two large bore peripheral intravenous lines, an arterial line, and a sheath introducer for volume resuscitation was planned. No epidural due to the emergent nature of the procedure. The fluid management strategy was for a restrictive fluid therapy approach with a balanced salt solution (lactated ringers solution—LR), minimal normal saline (only for blood transfusion) and colloid (5% albumin for significant blood loss until the transfusion trigger was reached). Intraoperative blood salvage was preferred in this circumstance where there is anticipated significant blood loss and there was no contraindication to use. The surgical plan was an open AAA repair with infrarenal cross-clamp due to location and size of the aneurysm.

Monitoring

Although strategies are emerging looking at restrictive fluid management as improving outcomes, no standard has developed on the ideal perioperative monitor. Traditionally arterial, central venous pressure (CVP) and pulmonary artery (PA) lines were used to guide fluid therapy and monitor hemodynamic performance. The CVP and PA catheters provide values which are shown not to be valid to judge ventricular preload (fluid status) in order to optimize cardiac performance [15]. They were good for trending and may still prove to be useful in that regard. Fluid responsiveness is the current basis for fluid management and optimization of cardiac performance. There is evidence of improved outcomes with restrictive or goal directed fluid therapy based on pulse pressure variation (PPV) and fluid optimization in surgical patients [16]. Pulse pressure variation is the difference between the highest and lowest pulse pressure divided by the average pulse pressure during the respiratory cycle while being mechanically ventilated. A similar parameter, stroke volume variation (SVV) is the difference between highest and lowest stroke volume divided by the mean stroke volume. A PPV > 13% or SVV > 10% indicates a fluid responsive state. These monitoring parameters are included in pulse wave contour analysis to determine continuous cardiac output (CO), PPV and SVV. Pulse wave contour analysis has some restrictions which includes the patient must be intubated on a tidal volume of 6–8 cc/kg, in sinus rhythm and have a closed chest. In a pig study by Biais et al., however this technology was shown to be inaccurate in AAA surgery due to aortic cross-clamping and unclamping [17]. Two additional human studies showed this technology as not valid in AAA surgery as well because of aortic cross-clamping and unclamping [18, 19]. Dynamic arterial elastance (Ea_{dyn}) is a parameter which may be used to assist in deciding between fluid bolus and vasopressor therapy for hypotension. This is defined as the ratio of PPV/SVV and describes arterial vasomotor tone in mechanically ventilated, preload-dependent patients [20, 21]. The elastance is defined by the change in pressure which occurs with a change in

volume and is a dynamic variable as opposed to the static variables historically used to assess volume, CVP and pulmonary artery occlusion pressure. Cecconi et al. provided evidence that dynamic arterial elastance is also valid in spontaneously breathing preload dependent patients to predict arterial pressure response to fluid challenges [22]. Dynamic arterial elastance could be useful in regard to predicting an increase in arterial blood pressure in response to a fluid challenge rather than just an increase in cardiac output which is the usual parameter measured with fluid loading. It is also being studied in predicting the potential decrease in blood pressure seen with weaning of norepinephrine in sepsis and post cardiac surgery vasoplegia [23, 24]. Not all studies support the predictive nature of dynamic arterial elastance Ea_{dyn} [25]. Having the ability to predict an increase in blood pressure with volume expansion would be an invaluable tool which could assist in preventing fluid overload which negatively impacts morbidity and mortality.

Other modalities exist as well. One study by Mannova et al. showed esophageal Doppler use in AAA repair may decrease complications, intensive care unit and hospital length of stay. Interestingly these patients received more fluid than the control group [26]. Transesophageal echocardiography is also used to estimate volume status and fluid responsiveness intraoperatively. Transthoracic echocardiography may be useful postoperatively for a static point in time and can be repeated serially to estimate volume responsiveness.

Our patient was taken to the operating room where American Society of Anesthesiologists standard monitors and an arterial line were placed and then he was induced and intubated with propofol and rocuronium without difficulty. Two large peripheral intravenous lines were then placed. A right internal jugular introducer catheter was placed under ultrasound guidance. There was no epidural catheter placed which is commonly done under elective circumstances. Incision was made. Dissection to gain control of the aneurysm proximally and distally were underway and at one point during the dissection, there was a rapid 2 liter blood loss prior to cross-clamping. This was managed with colloids, packed red blood cells and later cell saver blood.

Aortic Cross-Clamping

Open AAA surgery requires cross-clamping of the aorta in order to isolate and reconstruct the aorta at the location of the aneurysm. Aortic cross-clamping causes a series of physiological changes the extent to which depends on the location and duration of clamping. The physiological changes based on location of the clamp on the aorta are related to redistribution of blood flow which generally causes hypertension and increased systemic vascular resistance (SVR) without a change in heart rate. In our case, there was an infrarenal aortic cross clamp applied, however it is not uncommon to have a suprarenal or supraceliac clamp placed for more proximal

aneurysms. When a clamp is applied to the infrarenal aorta, non-sphlanchnic blood can be redistributed to the superior vena cava (SVC) thereby increasing preload and subsequently SVR and blood pressure or it can redirected to the sphlanchnic circulation without a significant increase in preload. The degree of diversion of non-sphlanchnic blood to the SVC depends on multiple factors including sphlanchnic vascular tone, anesthesia, clamp location and volume status. While the cross-clamp is applied, there are other physiological changes occurring. There is an increase in anaerobic metabolism distal to the clamp where the tissues receive diminished perfusion via collaterals. This causes an increase in lactic acid leading to a metabolic acidosis and build up of carbon dioxide which is washed out from the tissues upon reperfusion [27, 28].

Effect of the Aortic Cross Clamp on Other Organs.

The lungs can be injured by release of inflammatory mediators causing increased permeability and inflammation in the lung leading to non-cardiogenic pulmonary edema.

The kidneys are sensitive and commonly injured occasionally leading to temporary and even permanent dialysis. Approximately 7% of infrarenal abdominal aortic surgery patients have renal dysfunction. This incidence is higher with a suprarenal clamp. The mechanism is mostly due to acute tubular necrosis (ATN) from ischemia and reperfusion of the kidney [27].

The spinal cord is also at high risk given the potential involvement of the artery of Adamkewicz (AOA). It may be potentially occluded by an aneurysm or the repair leaving the spinal cord ischemic for a period of time which can lead to spinal cord injury and paralysis. Recall, the AOA is a single distal branch (often originating from thoracic spinal cord levels T9-T12) which supplies a large portion of the anterior spinal cord.

The intestines are similarly at risk for ischemia by low flow, injury to or ligation of the inferior mesenteric artery and hypogastric artery which can lead to colon and rectal ischemia. Supra celiac cross-clamping puts the entire sphlanchnic circulation at risk.

Cross-clamping in a patient with aneurysmal disease typically causes more hemodynamic effects than one with occlusive disease since in occlusive disease, the vessels have been narrowing over time with development of collateral circulation. The application of the cross-clamp occludes the remainder of the aorta with the collaterals increasing flow to accommodate whereas in aneurysmal disease, there is typically limited collateral development.

Renal Protection

Renal insult is a serious concern in aortic surgery as the application of an aortic cross-clamp will disturb renal blood flow. When a suprarenal clamp is applied, the kidneys will become ischemic for the duration of the cross-clamping time. While an infrarenal cross clamp does not cause ischemia of the kidneys by clamp location, there is disturbance in the character of the aortic renal flow which can cause a

transient rise in creatinine as well as an acute kidney injury (AKI) . The risk increases with suprarenal clamps for obvious reasons. In a pilot study by Brinkman et al., 20% of patients undergoing open AAA repair developed acute kidney injury. The study concluded that the only factor predicting postoperative AKI was length of time the cross-clamp was applied and the magnitude of intraoperative hypotension [29]. Efforts to protect the kidneys have been undertaken with both pharmacologic and nonpharmacologic interventions. While it is an attractive thought to have a renal protective drug, no one agent has yet emerged as effective. Many agents have been tried including N-acetylcysteine [30], dopamine [31], and mannitol, which may induce renal vasodilation and redistribute systemic blood flow to the kidneys, but none has proven effective [32–34]. Non-pharmacologic strategies center on prevention of hypotension, volume loading to protect renal perfusion and renal blood flow, avoiding nephrotoxic agents and strict glycemic control in an effort to avoid acute tubular necrosis which is the most common mechanism of injury. Additionally, cardiovascular support and stability coupled with recognition and management of postoperative intra-abdominal hypertension and rhabdomyolysis is critical.

The infrarenal aorta was cross-clamped with an increase in pulmonary artery filling pressures and blood pressure which was treated with nitroprusside to a moderate degree since the goal was to keep the blood pressure as high as reasonable to assure distal collateral pressure and flow. Nitroglycerin and nitroprusside are common agents used to manage increases in preload and afterload respectively. Our patient underwent an open repair of a right common iliac artery aneurysm with right internal iliac artery, external iliac artery and left common iliac artery repair; reimplantation of the inferior mesenteric artery (IMA) and closure of an aortocaval fistula from inside aneurysm sac.

Unclamping the Aorta

When the cross-clamped infrarenal aorta is unclamped, there is a significant decrease in SVR and concomitantly the blood pressure. This is due to distal artery vasodilation from the accumulation of acid metabolites, including lactate and carbon dioxide, which occurred during the time the aorta was cross-clamped. This leads to central hypovolemia as well as a reactive hyperemia which increases blood flow to the ischemic areas. The ischemic reperfusion injury can increase vascular permeability causing sequestration of fluid in the tissues, including the lungs, and the extracellular fluid space. Sequestration of excess fluid in the lungs, manifest as non-cardiogenic pulmonary edema, can adversely impact oxygenation because gas exchange at the alveoli is diminished. Efforts to minimize the effect of unclamping center on slow removal of the clamp to minimize rapid acid washout and abrupt change in SVR as well as with judicious use of fluids and pressors [27, 28].

Prior to the cross-clamp being removed, nitroprusside was titrated off and the patient was given a crystalloid fluid bolus to optimize preload. Phenylephrine was administered with a simultaneous decrease in volatile anesthetic to reduce vasodilation. Additionally, the clamp was slowly removed by the surgeon to minimize the expected immediate drop in systemic vascular resistance. The blood pressure was well preserved with these interventions. Once hemostasis was achieved, the surgical team proceeded to reapproximate the incision.

Fluid Management

Fluid management can impact upon post-operative parameters including cardiac morbidity, timing of extubation, ileus, and renal function. Control of postoperative edema promotes improved pulmonary function, especially with the potential for increased vascular permeability, less significant fluid shifts, improved wound healing and more rapid return of bowel function. Equally important, under resuscitation' is also deleterious as it will cause lactic acidosis, ischemia in the tissues, and increased cardiac stress (manifest as an increased heart rate with a decrease in stroke volume in an attempt to maintain cardiac output).

Traditionally, balanced crystalloid solutions are used for maintenance and resuscitation in major abdominal surgery, however saline is also frequently used. In this case, we elected to use lactated ringers solution (LR) for maintenance and replacement of insensible losses and albumin to replace blood loss until a transfusion trigger was reached [35, 36]. In a study of 15,802 critically ill adult patients receiving saline or balanced crystalloid (LR or Plasmalyte A) Semler et al. demonstrated there was decreased mortality, renal replacement therapy, and persistent renal dysfunction in the balanced crystalloid group [37]. Saline is well known to cause hyperchloremic metabolic acidosis with large volume infusion [38–40]. In another study comparing colloid and saline's effect on volume expansion and myocardial function in the setting of treating hypovolemic hypotension during cardiac and major vascular surgery, Verheij, et al. found that colloid fluid loading leads to a greater increase in preload and recruitable cardiac and LV stroke work indices due to increased plasma volume expansion and increase in plasma colloid oncotic pressure [41]. There is an increasing body of literature supporting restrictive or goal directed fluid management as supporting improved outcomes [1, 42, 43]. There is also, however literature against this approach as well. Myles et al. studied a restrictive versus liberal fluid management strategy during and up to 24 hours postoperatively in major abdominal surgery. The group found the restrictive regimen was not associated with a higher rate of disability-free survival and had a higher rate of renal disability than a liberal strategy [43–45]. In a study done by Kassim et al. on AAA patients using a liberal versus a restrictive strategy (12 ml/kg/hr. versus 4 ml/kg/hr) while optimizing oxygen delivery to maintain an oxygen extraction ratio estimate <27%, the

restrictive group had decreased major complications and hospital length of stay [46]. Another study by Piljic et al. compared restrictive and liberal fluid management strategies in minilaparotomy AAA and showed that intraoperative and postoperative restrictive regimens reduced postoperative morbidity [47]. McArdle et al. studied restrictive versus standard fluid regimens in elective open AAA repair and found that a restrictive approach decreased major complications and hospital length of stay [2]. In an effort to identify the mechanism of goal directed fluid therapy improvements, Funk et al. studied restrictive versus standard therapy in AAA and measured cytokines as markers of the inflammatory response. They found no difference in the inflammatory response despite fewer complications and improved hemodynamics in the restrictive group [48]. While most of these studies show a decrease in major adverse events and morbidity, many were underpowered to detect differences in mortality.

Our patient had the following intake and output for the procedure Table 28.2.

The patient was transferred to the SICU post operatively after an eight hour surgery where he remained intubated overnight to assure hemodynamic and hematologic stability. His sedation was weaned and he moved all 4 extremities to command. He remained hemodynamically stable. His hemoglobin and hematocrit were 9 g/dl and 27% respectively, platelets 125 k/ μL and INR was 1.4. He was extubated uneventfully in the early morning of postoperative day 1. In the immediate postoperative period he had a transient increase in his creatinine peaking at 1.93 mg/dl while maintaining an adequate urine output and his electrolytes remained within normal limits. His hemoglobin remained stable. His intravenous fluids were maintained at 75 ml/h. for postoperative day 1 and they were stopped on postoperative day 2. His troponin was checked as an indicator of myocardial injury and was not elevated postoperatively. His ECG was unchanged postoperatively. He had no issues indicating colonic ischemia which is a risk with the inferior mesenteric artery reimplantation. His nasogastric tube was removed on postoperative day 2 and he was taking sips of clears.

Table 28.2 Intake and output for our patient in the operating room

	Intake	Output
Crystalloid (LR)—ml	4000	–
Colloid (5% albumin)—ml	1000	–
Cell Saver Blood—ml	1800	–
Packed Red Blood Cells (PRBC)—units	4	–
Fresh Frozen Plasma (FFP)—units	2	–
Platelets—units	1	–
Urine output—ml	–	1250
Estimated Blood loss—ml	–	5000

Postoperative Course

The effects of perioperative fluid overload are manifest in the postoperative period as well. Lobo et al., in a study of colon surgery patients, showed increased volume in the postoperative period led to delays in return of bowel function and prolonged hospital length of stay [49]. An additional postoperative consideration is the cardiac status of the patient. The VISION study included 15,133 patients having noncardiac surgery to determine the relationship between peak troponin in the first 3 days postoperatively and 30 day mortality. The investigators concluded that elevations in troponin as little as 0.02 ng/ml postoperatively was associated with 30 day mortality [50].

Conclusion

Fluid management of the vascular surgery patient can be complex in the dynamic perioperative period. Close attention to particular needs at each stage of the procedure will ensure improved outcomes. Although there is some conflicting evidence, it appears that a restrictive approach using isotonic crystalloids with appropriate use of colloids and blood products will enhance the patient's recovery. This patient was extubated without incident and had early return of bowel function which are two positive outcomes of restrictive fluid therapy. Fluid should be regarded as a drug with an appropriate type, dosage and duration. Other important issues such as the physiology of aortic cross-clamping and unclamping, hemodynamic monitoring, and renal protection should be considered in planning for patient care. Much more work needs to be done to delineate the optimal strategy for perioperative management of the patient undergoing major vascular surgery.

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Case Scenario for Fluid Management in Obstetrics

29

Ahmed Reda Taha

Abstract

During pregnancy, labor, and the postpartum period, the physiological, hormonal, biochemical, and physical changes represent the adaptations that have a significant impact on perioperative fluid management. Anesthesia providers play a critical role in interpretation and decision making to select the most appropriate type and time for fluid administration, based on available cardiovascular and hemodynamic parameters, these parameters derived from clinical assessment and monitoring. Presence of additional comorbidities encourages the involvement of the multidisciplinary team to ensures favorable maternal and fetal outcomes (Cove, Pinsky, Best Pract Res Clin Anaesthesiol. 26:453–462, 2012).

Key Points

- The changes in fluid dynamics occurring during Pregnancy and labor carry a significant impact on fluid management.
- Standard monitoring should be applied before commencing any anesthetic technique and should be considered to escalate to more invasive procedures as dictated per patient hemodynamics.
- Utilize maternal and fetal parameters with high validity to evaluate fluid administration.
- Consider fluid Co-loading or Preloading together with left uterine displacement to prevent hypotension in parturient receiving spinal anesthesia for a cesarean section.
- Dynamic assessment of maternal cardiovascular function can detect the effects of postural change on cardiovascular indices in pregnancies.

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- Restricted fluid infusion of crystalloids is appropriate in hypertensive diseases of pregnancy, keeping in mind the maintenance of perfusion parameters.
- Timing of fluid administration amount and type, remains controversial.
- Utilize personalized Goal directed fluid therapy targeted at optimizing maternal stroke volume using PiCCO technology/PLR + TTE.
- Peripartum hemorrhage required adequate replacement of intravascular volume and good surgical hemostasis to control and reduce the consequences of bleeding.
- Maternal fluid management may have secondary effects on the fetus, but these effects may be limited.

Perioperative Fluid Management

Pregnancy represents a different state of body fluids dynamics, where body fluid composition starts changes from conception to the time of delivery. In recent times, individualized goal-directed therapy has become popular and more effective in perioperative fluid management. The target values for a cardiac index, oxygen delivery, and oxygen consumption can be achieved by appropriate use of fluids and inotropes in the perioperative period. The role of peri-operative fluid administration is to optimize a patient's cardiac function and ultimately, oxygen delivery.

Several clinical reviews support the use of individualized GDT in perioperative settings. Especially with the increasing availability of appropriate monitoring equipment which ensure meticulous fluid management during this period and prevent any risk to the mother or the fetus [1].

Fluid Homeostasis During Pregnancy

Pregnancy results in several physiological changes in fluid dynamics, which have a significant impact on fluid management. By the term, total blood volume increases by 45%, and red cell volume increase by 30% and this differential lead to a condition called "physiological anemia of pregnancy" or "hemodilution of pregnancy" (this changes illustrated in Fig. 29.1). Increase in blood volume and fall in colloid osmotic pressure predisposes the pregnant patient to a higher risk of developing pulmonary edema, especially during fluid loading [2]. Table 29.1 shows summaries of Hemodynamic Values and Changes During Pregnancy.

Clinical Case Scenario

23 years old G2 P0, pregnant 32 weeks patient presented with severe right upper quadrant pain that started 3 hours ago, she was fully conscious, oriented, and alert. The patient continued to have symptoms with acute worsening of the epigastric pain 2 hours before arriving.

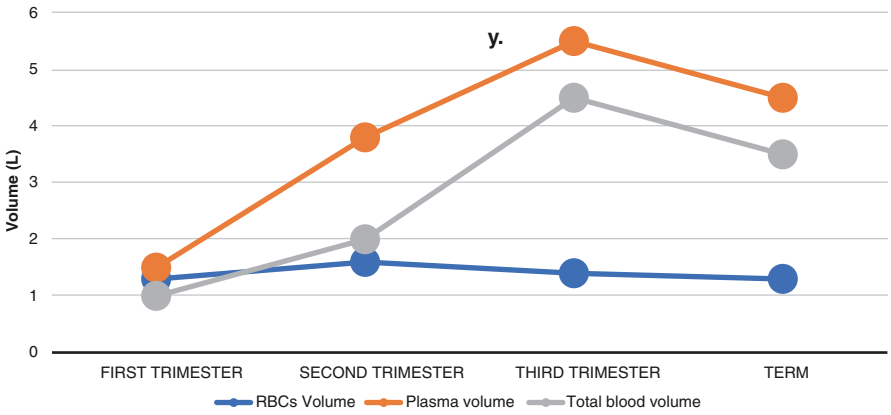

Fig. 29.1 Changes in intravascular fluid volume (blood volume), plasma volume, and RBCs volume during progression of normal pregnancy

Table 29.1 Hemodynamic values and changes during pregnancy

	Non pregnant	First trimester	Second trimester	Third trimester
Blood volume (mL/kg)	65	70	85	90
Albumin (g/dl)	7.8	7.6	7.4	7
Plasma volume (mL/kg)	40	45	55	60
Cardiac output (L/min)	4.3	5.7	6	6.2
Stroke volume (mL)	65	75	85	80
Heart rate (beats/min)	70	75	80	80
CVP (mmHg)	5	5	5	5
SVR (dyne/cm/sec5)	1500	1200	950	1200
COP (mmHg)	21	19	18	17

Abbreviations: *CVP* central venous pressure, *SVR* systemic vascular resistance, *COP* colloid oncotic pressure
Source: From Refs. [1, 3–8]

1. On admission she is not feeling any contraction and no history of fluid loss or vaginal bleeding
2. Positive perception of fetal movements
3. Hypertension—on Methyldopa
4. Developed seizure after 20 min of admission lasted for 40 s
5. Received hydralazine 20—on 2-l nasal mg IV and started on Nasal cannula oxygen as needed.
6. Recorded to be disoriented and unaware in ER, with drop of saturation to 91% mandate intubation.
7. Fetal heart tones detected 135 beat/min

Preoperative vitals: blood pressure (BP), 200/102 mmHg; pulse, 90; height, 147.3 cm, weight, 60.1 kg; body mass index (BMI), 27.70 kg/m^2; SpO2, 96%.

How should we approach perioperative fluid management in such clinical scenario?

When the patient reach OR there is multiple clinical consideration needs to be highlighted before administration of any fluids.

1. physiological changes and monitored physiological parameters
2. Hypertensive disorders of pregnancy and associated hemodynamic changes
3. requirement of antihypertensive medication to control blood pressure
4. eclamptic seizures and cerebral disorders
5. associated coagulation disorders with Pregnancy Induced Hypertension
6. Proposed surgical procedure and anesthetic approach.

General Preparation for Caesarean Section

Patients should, wherever possible, have a full pre-anaesthesia assessment in the Preoperative Clinic or on the inpatient unit prior to elective Caesarean Section and, if time permits, prior to emergency caesarean section.

In case of emergency Caesarean Section where time does not permit assessment in the inpatient or outpatient setting, the pre-operative assessment including the results of investigations will be conducted and recorded in the Operating Room.

Antacid regimen for Caesarean Section: 30 mL of 0.3 M sodium citrate prior to induction in Operating Room and 10 mg of intravenous (IV) metoclopramide or 50 mg of IV ranitidine can be considered in patients with full stomach; however it is NOT a priority.

IV access and co-loading Secure IV access with size 16G or 14G (if patient at risk of massive hemorrhage) once the woman arrives in OR. Infuse approximately 1000 mL Hartmann's solution immediately after the spinal anesthesia is administered (co-loading) except for woman with pre-eclampsia where IV fluids will be titrated according to blood loss and vital signs. Where applicable, a pressure bag can be used to increase the rate of the infusion [9].

Requirement for Monitoring

Standard monitoring should be applied before commencing any anesthetic technique. This includes ECG, non-invasive blood pressure measurements and pulse oximetry. Invasive blood pressure measurement may be needed in some maternal conditions such as (but not limited to): severe preeclampsia, expected massive obstetric hemorrhage as in placenta previa and accrete cases [9].

Intraoperative Anesthetic Management

Ultrasound guidance for spinal anesthesia: The use of ultrasound to guide spinal and epidural anesthesia should be encouraged for all Caesarean Sections. In grade I Caesarean Section the decision to use the ultrasound depends on the indication and

the experience of the anesthetist with the use of the ultrasound. The following information is provided by the pre-procedure scan: (1) Identification of the midline, (2) Determination of the level of the injection, (3) Identification of the depth of the space.

Maternal positioning is dictated by the anesthetist's preference, maternal comfort and the baby's condition. The sitting position is the position most commonly used. In either position, sitting or lateral, it is important for the mother to flex the spine to open up the intervertebral spaces [9].

Single shot spinal anesthesia: Using a pencil point 25G/26G spinal needles and after lidocaine 2% for skin infiltration, 2.5–3 mL 0.5% heavy bupivacaine (12.5 mg to 15 mg) + 20 mcg fentanyl. Phenylepherine is the most commonly used vasopressors to prevent spinal induced hypotension. The infusion is to be started at a rate of 50 mcg/min for the first 3 min, unless the blood pressure is >20% of the baseline reading. After 3 min, the rate is to be titrated to maintain baseline systolic blood pressure. The infusion should be on-going until the delivery of the baby. The patient must be continuously monitored for bradycardia or arrhythmia while the infusion is in progress.

After performing the spinal block, position the mother immediately on her back in the Trendelenburg position with the head slightly up (use a pillow under the head and shoulders) and the bed tilted to the left side. Maintain this position until surgery is started. Commence an IV infusion of crystalloid colloid. Check motor and sensory block after 5 min. There should be loss of cold sensation to ice at T4 and to touch (use blunt needle) at T6, bilateral sympathetic block (warm, dry feet) and bilateral motor block (just able to move toes). If the block extent is below T4, turn the patient into the right lateral position and place the head down if needed [9].

Combined Spinal-Epidural (CSE)

Equipment needed: Either a combined spinal-epidural set is to be used or separate sets, a 16G epidural set and an individual Pencil point 27G spinal needle.

Drugs needed: Heavy bupivicaine 0.5% 1.5–2 mL + fentanyl 20 mcg (100–300 mcg morphine may be added for postoperative analgesia). The epidural component of the block will increase the block height if injected immediately after the spinal [9].

To monitor the hemodynamic status during the C.S in such critical scenario radial arterial catheter should be considered prior to induction of general anesthesia for patients with severe preeclampsia based on blood pressure, if time permits, to provide continuous blood pressure monitoring and rapid response to adverse changes, especially during rapid sequence induction and during emergence [10].

Radial artery catheters are not routinely placed for hemodynamic monitoring during labor for patients with preeclampsia. However, radial artery catheterization is a low-risk procedure [4] that may be beneficial for continuous blood pressure monitoring, and facilitates blood sampling [11]. Placement of an arterial line should be considered in the following situations:

- Persistent, severe hypertension (e.g., systolic blood pressure > 160 or diastolic blood pressure > 110) refractory to treatment
- Use of vasoactive infusions to control blood pressure-Need for frequent blood sampling (e.g., patients with coagulopathy, hemorrhage, severe renal or hepatic dysfunction), particularly for patients with difficult peripheral venous access
- Need for frequent arterial blood gas monitoring (e.g., patients with pulmonary edema and hypoxia)
- For use of a minimally invasive cardiac output monitor to guide hemodynamic management [10].

Additional monitoring with Central venous catheters (CVCs) and pulmonary artery catheters (PACs) are rarely used in parturient with preeclampsia. Indications for placement are similar to those for patients without preeclampsia, including difficult peripheral venous access, central administration of vasoactive infusions, and measurement of cardiac function and/or preload. However, complication rates for central line placement are relatively high in patients with severe preeclampsia [5, 12] and there are no randomized trials to support the use of CVCs [13]. Placement of a CVC or PAC takes time, and should not delay delivery for patients with severe preeclampsia. Central venous pressure correlates poorly with pulmonary capillary wedge pressure in patients with preeclampsia [6, 7]. Therefore, a PAC should be placed if measurement of preload is the primary objective [8].

Nevertheless, the evidence currently does not support plasma volume expansion as it may promote pulmonary edema due to capillary leakage with no consistent effect on the outcome. The current era of fluid restriction may have accounted for the decline in maternal mortality due to pulmonary edema with none reported in the most recent Enquiries into Maternal Death from the United Kingdom [14].

Parturient with severe preeclampsia is poorly tolerant to Volume over load if the ventricular dysfunction is present and is also sensitive to the sympathetic blockade. Three possible etiologies of pulmonary edema have been suggested in preeclampsia: (I) left ventricular failure (II) pulmonary capillary leak and (III) reduced colloid oncotic pressure. Colloid oncotic pressure (COP) is normally in the range of 25–28 mmHg. It is less in pregnancy, 22 mmHg at 34–36 weeks, about 18 mm Hg after delivery and may fall as low as 14 mmHg in pre-eclampsia [15]. Cesarean delivery, which is usually instituted to terminate a pregnancy in such parturient, is currently accessible to be performed under combined spinal-epidural anesthesia (CSEA) [16]. Spinal anesthesia is safe for lower segment cesarean delivery in stable eclamptic patients to avoid risks of general anesthesia [16, 17].

Discussion and Rational

Primary goal of fluid management is optimizing maternal, uteroplacental, and fetal perfusion during pregnancy and delivery, reductions in blood pressure can resulted in fetal compromise. Limiting the effects of central neuraxial blockade on maternal hemodynamics is crucial step. The fluid management for parturients during labor

analgesia, cesarean section, and the postpartum period, and in special pregnancy states, can now be evaluated with caution, utilizing maternal and fetal parameters with high validity to evaluate fluid administration [18].

Fluid Management in Normal Labor

The epidural and combined spinal-epidural (CSE) techniques used for labor and delivery analgesia usually employ an opioid with a low-dose local anesthetic to initiate and maintain a dermatomal sensory level of approximately T10. As such, the incidence of hypotension with either technique is low, with the CSE technique being no more likely to lead to hypotension [19]. The prevalence of hypotension following the use of such anesthetics has been noted to be less in parturients in labor than those presenting for elective cesarean section [20] In part, this difference has been attributed to laboring parturients receiving continuous IV hydration during labor versus elective cesarean delivery patients being NPO.

Fluid administration prior to epidural analgesia has proved to have no real effect. In comparing 0.5 L and 1 L LR with no fluid bolus prior to epidural analgesia, no difference in the incidence of hypotension was observed (the actual incidence of hypotension was not noted) [21]. In a similar study comparing 0.5 L or 1 L LR prior to epidural analgesia (10 mL of 2% lidocaine with epinephrine 1:200,000) in healthy laboring parturients [22], no difference in the incidence (4%) or severity of hypotension between the two groups was identified. In addition, the 1 L fluid preload produced a delay in the initiation of the epidural technique and a slowing of uterine contractions.

The limited hemodynamic sequelae of epidural and CSE labor analgesia techniques suggest that IV fluid preloading prior to these techniques is not necessary for healthy laboring parturient.

Fluid Management in Caesarean Section

Usually, pregnant females are exposed to rapid intravascular fluid fluctuations during cesarean deliveries. Spinal anesthesia is used frequently for cesarean deliveries because of its rapid onset, minimal risk of anesthetic toxicity and negligible transfer of the drug to the fetus, as well as a little risk of failure of the block. However, a higher incidence of hypotension is a significant disadvantage. Prevention of spinal anesthesia-induced hypotension is of utmost importance as the life of the mother as well as the fetus is at risk. Several methods and techniques like intravenous fluid boluses, left uterine displacement, prophylactic vasopressors and utilizing compression stockings onto the lower extremities have been tried and utilized in daily routine obstetric practice [23].

Historically, hypotension developed due to neuraxial anesthesia overcome by adequate iv fluid infusion and left uterine displacement. This concept was originally explored earlier, By contrast, vasopressors, including phenylephrine, levarterenol,

and angiotensin, restored only maternal blood pressure without correction of uterine perfusion. Subsequent work has questioned the success and role of fluid preloading in preventing adverse hemodynamic sequelae of neuraxial blockade in parturient [21, 24–27].

Recent studies focused on spinal anesthesia for cesarean delivery, where uterine aortocaval compression and the rapid onset of hemodynamic effects are observed. Such trials are difficult to judge the types and volumes of fluids and use of vasopressors, A lower incidence of hypotension (5–63%) has been observed following the use of epidural anesthesia for cesarean delivery, most likely owing to the slower onset of blockade, [21, 28, 29].

Crystalloid preloading has been noted to reduce the incidence of hypotension in this population; however, a high incidence of hypotension (50–70%) is still observed [25], with most patients requiring treatment with vasopressors to maintain blood pressure [30]. For example, when 20 mL/kg of crystalloid (Plasma-Lyte L) administered over 15 to 20 min was compared to no preload, the incidence of hypotension in parturient scheduled for cesarean delivery was reduced (55% vs. 71%, respectively). Which didn't show any changes even after application of ephedrine, six of nine studies indicated a trend or a reduction in the incidence of hypotension with crystalloid preloading prior to spinal anesthesia for cesarean delivery. The crystalloid type, volume, rate of administration, and timing of administration are relevant determinants that should be discussed.

One issue of controversy is the use of glucose-containing fluids. Subsequent investigations have failed to demonstrate a benefit in giving pre-operative dextrose prior to cesarean section. Parturient randomized to receive normal saline with and without dextrose 5% at 125 mL/h. for two hours prior to delivery had the same incidence of hypotension [31]. The overall incidence of hypotension was 67% despite an IV preload with 15 mL/kg of fluid in both groups. Although maternal hypoglycemia was observed in 17% of the parturient, most likely reflecting a dilutional effect, dextrose infusions immediately prior to delivery should remain less than 6 g/h. to prevent fetal hyperglycemia and hyperinsulinemia, followed by neonatal hypoglycemia and jaundice [32]. A dose of 20 mL/kg of crystalloid given over 10 versus 20 min prior to a spinal anesthetic for elective cesarean section resulted in significant increases in CVP with no alterations in the incidence of hypotension [24].

The amount and type of fluid utilized does appear to be important when longer procedure considered, volume preload effect is achieved when it create enough change in cardiac output at the time of the administration of the spinal anesthetic. This appears most readily achievable with colloid solutions in amounts greater than 1 L. The perception that crystalloid fluids have short intravascular half-lives encouraged investigation into the use of colloid solutions to prevent spinal anesthesia-induced hypotension. Initial studies using combinations of crystalloid and colloid solutions achieved mixed results with reduction of hypotension from 33% to 0% [18].

In addition, the use of 1 L of crystalloid (Hartmann's solution) versus 0.5 L of Hartmann's with 0.5 L of colloid prior to epidural anesthesia for cesarean section was associated with a reduction in hypotension from 45% to 5% [33]. Given the

evidence showing harm from synthetic starch-based colloids, we used 5% albumin as the primary colloid solution.

Traditionally, 15 degrees of left uterine displacement has been recommended for pregnant patients to reduce aortocaval compression ("supine hypotension syndrome"), which occurs in the supine position when the uterus is at or above the umbilicus. A foam or wood wedge, pillow, or rolled blanket may be used, or the table can be tilted, or the uterus can be manually displaced [34]. Uterine displacement at cesarean delivery improves neonatal acid-base status. A systematic review published in the year 2013 was not able to determine the optimum method or maternal position [35]. Magnetic resonance imaging (MRI) examination of aortic and inferior vena cava volumes in pregnant and nonpregnant peers have shown that inferior vena cava volume, but not aortic volume, is influenced by patient position; specifically, a left-lateral tilt of at least 30 degrees is needed to improve vena cava volume. There is limited evidence to support or clearly disprove the value of the use of tilting or flexing the table, the use of wedges and cushions or the use of mechanical displacers. A left lateral tilt may be better than a right lateral tilt and manual displacers may be better than a left lateral tilt but larger studies with more robust data are needed to confirm these findings [36]. In a late third-trimester healthy pregnancy, both change from the supine to a sitting position, and passive leg raising associated with an increase in preload and subsequent increase in cardiac output and stroke volume and a decrease in total peripheral resistance index [37].

To assess maternal functional hemodynamics in pregnant women at 35–37 weeks' gestation, Study conducted to evaluate the effect before and after passive leg raising in the left lateral position. On comparing the changes in pregnant ladies that subsequently developed pre-eclampsia or gestational hypertension with those that remained normotensive, dynamic assessment of maternal cardiovascular function can detect the effects of postural change on cardiovascular indices which is similar but less marked than in normotensive pregnancies [37].

Liang et al., in his prospective observational cross-sectional Study, involved 53 pregnant women, he assessed preload reserve by measuring the SV and CO during baseline and 90 degree after PLR simultaneously by echocardiography and statistically significant correlation between impedance cardiography and Doppler echocardiography for measuring preload reserve [22].

Building on the potential use of aortic VTI, a recent report described the use of carotid blood flow (CBF) measurement in the carotid artery to predict fluid responsiveness. This approach measures the diameter of the carotid and carotid VTI. A ΔCBF of 20% after passive leg raising predicted an increase in cardiac output with 94% sensitivity and 86% specificity [38] (Fig. 29.2).

Hemodynamic Monitoring in Obstetric Critical Care

There are no current evidenced-based recommendations for CO monitoring in critically ill obstetrics patients. Two recent case reports provide discussion points for the choice of hemodynamic monitor in the high-risk population.

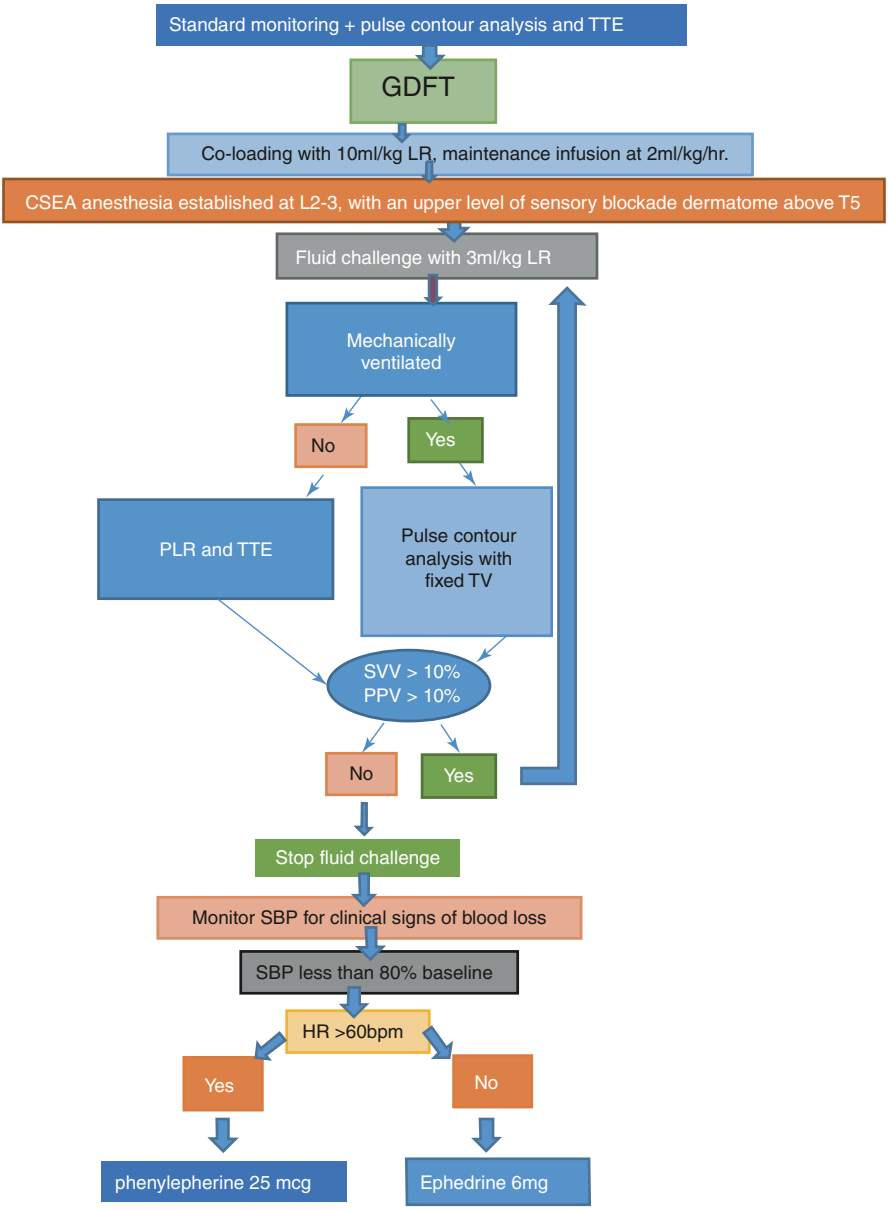

Fig. 29.2 Goal directed fluid therapy targeted at optimizing maternal stroke volume using PiCCO technology/PLR +(TTE or USCOM)

Lorello et al. [39] report the management of a patient with peripartum cardiomyopathy and severe left ventricular systolic dysfunction with an ejection fraction less than 20%, and pulmonary congestion. They used an arterial line and a noninvasive monitor, NICOM, during delivery. The authors highlight the importance of continuing the hemodynamic monitoring, as the patient deteriorated postpartum, and a PAC was placed. Many practitioners would prefer invasive monitoring from the outset in such a critically ill patient.

Schiraldi et al. [40] used continuous transesophageal Doppler monitoring (CardioQ) to guide fluid and overall management during a cardiovascular disease complicated by severe hemorrhage. This case report also shows that there should be a low threshold for the use of invasive monitoring in high-risk obstetric patients and that intra-arterial monitoring is obligatory [41, 42]. Recommended monitors in critical care include LiDCO plus, PiCCO and USCOM [11]. The PAC should be reserved for use in multiple organ failure, where mixed venous saturation measurements may be of value, and occasionally in severe pulmonary hypertension [42].

Respiratory variations in inferior vena cava (IVC) diameter have been shown to be an excellent tool for assessment of a patient's intravascular volume.

The IVC is easily visualized via ultrasonography. From the subcostal long axis view, the probe is tilted to the right of midline and rotated 90° counterclockwise, and the IVC can be visualized. If one has trouble finding the IVC, the hepatic veins can be followed until they terminate into the IVC. Care must be taken to ensure that the IVC is not confused with the aorta. Once an adequate view of the IVC in long axis is found, M-mode should be activated. The M-mode cursor should be positioned 2 to 3 cm from the right atrium and perpendicular to the vessel. Vigilance is needed so as not to inadvertently include the hepatic vein. The sweep speed of the M-mode should be decreased to allow for more time and respiratory cycles to be captured. The diameter of the IVC is then measured. If the difference between the maximum and minimum diameter(collapsibility [cIVC] in spontaneous breathing and distensibility [dIVC] if mechanically ventilated), normalized to their mean, is more than 12% in dIVC and 40% in cIVC, then the patient is likely to have a favorable hemodynamic response to a fluid bolus [43]. The ability of this measurement to predict fluid responsiveness in a patient with spontaneous breathing effort via cIVC, during small tidal volumes, or other evidence of cor-pulmonale remains less clear. The right lateral ultrasound view as a practical alternative to subcostal view has been successfully used to estimate the diameter of IVC in pregnant women [38, 43] (Fig. 29.3).

Intermittent use of transthoracic or transesophageal echocardiography, in ventilated patients, is indicated to identify or eliminate structural abnormalities, quantify ventricular function, and guide fluid therapy. However, continuous invasive hemodynamic monitoring remains an essential adjunct in selected patients, particularly when accurate measurements of pressure and flow are required [44].

Further assessment of Extravascular Lung water EVLW by a simplified lung ultrasound approach can be used as a reliable noninvasive bedside tool to predict pulmonary fluid burden. Caltabeloti et al. demonstrated the ability of lung ultrasound to define a fluid-tolerant state. In their study of patients with shock and

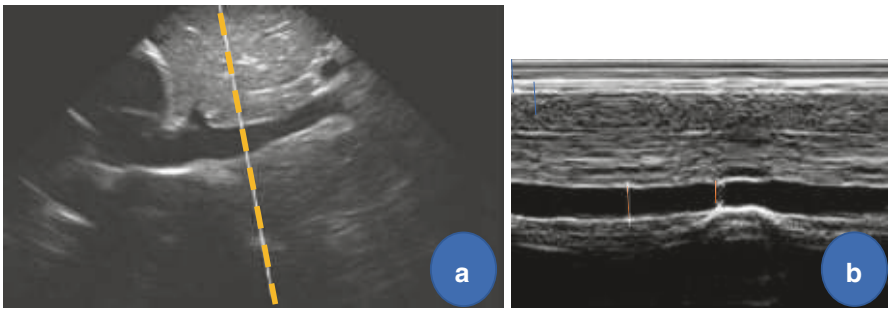

Fig. 29.3 Measurement of the inferior vena cava (IVC) caval index. (**a**) Long axis view of the IVC. (**b**) The diameter is measured with M-mode 2–3 cm distal to the confluence of the hepatic vein and IVC

ARDS, fluid loading produced only a transient improvement in hemodynamics and oxygenation but worsened interstitial edema, as demonstrated by lung ultrasound [38].

Based on recent studies of monitoring coagulation to restrict blood and blood products transfusion, TEG and ROTEM can provide early feedback to care providers about crucial changes in the maternal hemostatic profile during Postpartum hemorrhage (PPH). TEG and ROTEM can be considered for rapid hemostatic assessment during PPH, and these technologies have been endorsed in guidelines from the Obstetric Anesthetists Association (UK) [21], the European Society of Anesthesiology [34], and the American Society of Anesthesiologists [25].

Back to Case Scenario

Patient underwent uneventful procedure, delivery of 1000 gm male infant Apgar's 1,7. Cord blood PH.7.29, patient hemodynamic profile. HR 100, BP135/90, SATs 100%, Urine output is excellent, serum lactate 1.1 mmol/L, SCVO2 65%.

Fetal Consideration

Maternal fluid management can have a secondary effect on the fetus. Investigations with parturient demonstrated that an acute increase in maternal vascular volumes does not promote fluid transfer into fetus per se. Nevertheless, an acute decrease in maternal colloid oncotic pressure with the administration of hypotonic solutions can cause fluid shifts into fetus as evident by the decrease in fetal plasma osmolarity and increase in fetal urine flow. This appears to demonstrate that maternal oncotic pressure is more responsible rather than vascular hydrostatic pressure changes for determining the fluid shifts into the fetus. When comparing colloid and crystalloid loading in pregnant individuals, no significant changes in fetal myocardial contraction and left ventricular (LV) function was reported so far [18]. In a

randomized controlled trial, Tawfik et al. found that neither crystalloid co-load nor colloid preload can totally prevent hypotension and should be combined with vasopressor use for an optimal neonatal outcome [33]. Tercanli et al. also assessed the effect of crystalloid preloading and co-loading in parturient and found that there are no significant differences in neonatal outcomes by APGAR scores and cord blood pH [45]. Acute fetal stress is a sensitive marker of neonatal outcome and is represented by umbilical cord pH and PaCO2 values. Jain K et al. in their randomized study emphasized the importance of fetal blood gas measurements and the effect of vasopressors on it. The author suggested that the use of a higher dose of phenylephrine (>0.5 mcg/kg/min) is associated with umbilical cord pH>7.2 following elective cesarean deliveries [46]. A meta-analysis of twenty trials to investigate fetal acidosis with the use of ephedrine and phenylephrine, better control on hypotension with both the drugs were found, but with decreasing the risk of fetal acidosis under phenylephrine prophylaxis [47]. Recent studies are showing promising results for norepinephrine as an ideal vasopressor agent during cesarean deliveries. Mild beta agonist action of norepinephrine favors its use as a more suitable vasopressor than phenylephrine, which is associated with bradycardia in some situations. There is no significant difference in neonatal outcome when comparing phenylephrine and norepinephrine. More well-constructed randomized trials are needed to enlighten norepinephrine in the treatment of post-spinal hypotension in cesarean deliveries [48]. Although not uniformly observed to be different from the infants of parturient undergoing vaginal deliveries, infants born to mothers undergoing cesarean deliveries were found to have low colloid osmotic pressure. Among the other variable believed to affect fetal colloid osmotic pressure are the amount of maternal fluid administration, intraoperative fluid therapy is also have a significant effect on fetal colloid osmotic pressure [47]. Watson J et al. suggested that the restricted IV fluids policy did not affect infant weight loss during the delivery period. His exploratory analyses showed that breastfed new-born weight loss increases when intrapartum volumes infused are >2500 ml. The anesthetist should be vigilant when to consider to infuse volumes of IV fluid during intrapartum or surgery as collective evidence shows a contribution to early newborn weight loss in the first 48 hours of life [49].

Conclusion

The physiological, hormonal, and mechanical changes associated with different stages of pregnancy represent adaptations that have a particular impact on fluid management. Although a better understanding of these alterations has resulted in enhanced guidance during pregnancy and labour, the value of fluid preloading before or during central neuraxial blockade for analgesia and anesthesia remains controversial. Several studies support the use of crystalloid and colloid solutions as a preload fluid; however, differences in the definitions of hypotension, regional anesthetic techniques, and the amount, type and timing of fluid administration make decision a pit difficult.

The use of the left uterine displacement, attentive monitoring, personalized goal directed fluid management and early treatment of the hemodynamic effects of epidural and spinal techniques with fluid and vasopressors remain the most effective means of ensuring favourable fetal and maternal outcomes.

Particular disorders observed with pregnancy, such as preeclampsia, Eclampsia, gestational diabetes, and maternal haemorrhage requires special attention to the type and amount of fluid and blood product administration.

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Index

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