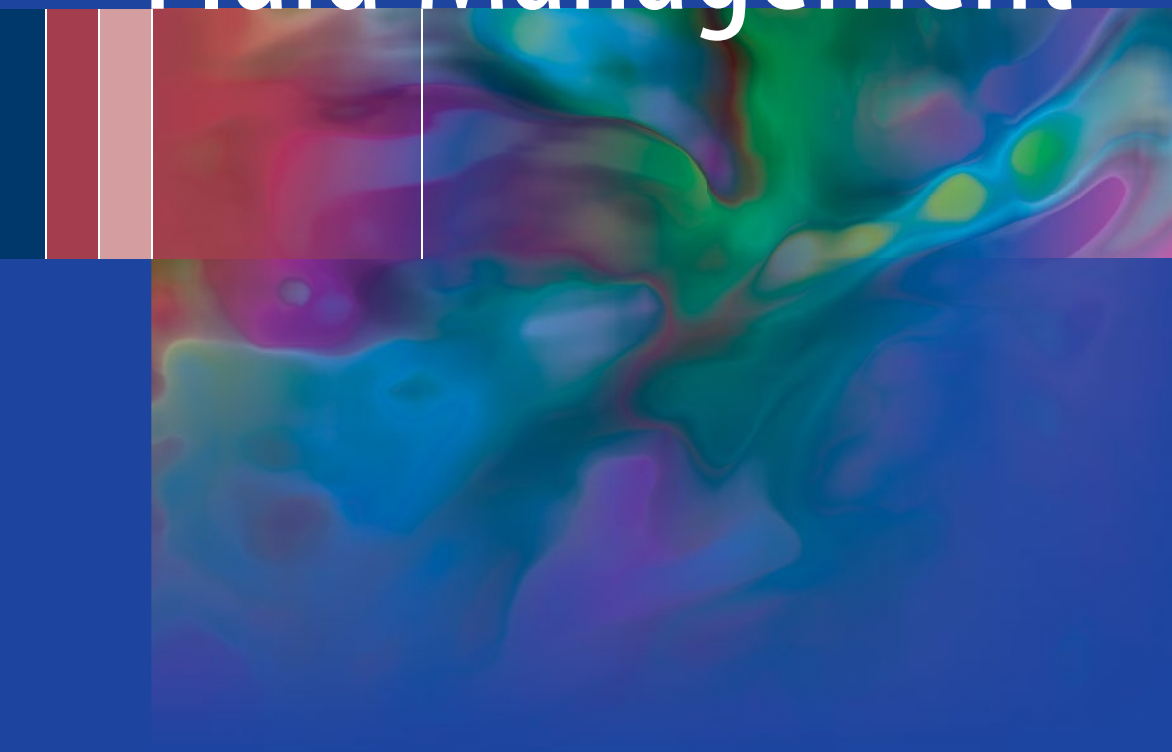
Ehab Farag · Andrea Kurz
Editors

Perioperative Fluid Management



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Editors
Ehab Farag
Professor of Anesthesiology
Cleveland Clinic Lerner College of Medicine
Director of Clinical Research
Staff Anesthesiologist
General Anesthesia and Outcomes Research
Cleveland Clinic
Cleveland
Ohio
USA

Andrea Kurz
Professor of Anesthesiology
Cleveland Clinic Lerner College of Medicine
Chairman of General Anesthesia
Cleveland Clinic
Cleveland
Ohio
USA

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To my daughter Becky for her compassionate, listening ear, and assistance in many of my publications.

– Ehab Farag

Foreword

Perioperative fluid management has been a debated topic for decades within the anesthesia, surgical, and critical care literature. The "classic" approach to fluid administration was based upon the duration of fasting, patient weight, duration of surgery, and extent of tissue disturbance. The high degree of evolution that has occurred on this topic is evidenced by perusing the contents of this book.

Drs. Ehab Farag and Andrea Kurz have assembled an incredible group of recognized authorities and experts in this field. Collectively, they have amassed one of the world's most comprehensive collections of evidence-based literature that supports the newest concepts and approaches to perioperative fluid management. Yet this book also provides a true historical perspective, beginning with the contribution of Dr. Elizabeth Frost, followed by chapters on the revised Starling principle and functions of endothelial glycocalyx. The content of this book is deep and broad in discussing all aspects of perioperative fluid management, thorough, and comprehensive. No "stone is left unturned" in this discussion.

I have no doubt that this book will be used as a great reference for other academic endeavors in this field, making it a "must read" and necessary inclusion to the library of every anesthesiologist, surgeon, and critical care physician caring for perioperative patients.

The overall design of this book is two parts. The first part covers the overall process, techniques for monitoring and management, restricted vs liberal administration strategies, crystalloid vs colloid, patient outcome, and the role of fluid management in enhanced recovery protocols. The second part provides a case-based approach to fluid management in specific patient scenarios, broadly characterized as abdominal, orthopedic, neurological, and septic shock.

The topic of perioperative fluid management has important implications on morbidity, mortality, enhanced recovery, and perioperative outcomes. This book comes at a time when financial pressures are closely linked to patient outcomes with the evolution of bundled-payment models. A rational, evidenced-based, best practice approach to fluid management can have a significant impact upon overall patient outcomes and hence is a topic worthy of complete understanding in the manner in

which Drs. Farag and Kurz have undertaken. They are to be congratulated for their outstanding contribution to the literature.

On a personal note, I am proud to be associated with the many authors of this book who work at the Cleveland Clinic. Their outstanding contributions to this textbook are a testament of their dedication and daily contribution toward patient care that allows our institution to care for a wide variety of critically ill patients within many surgical subspecialty areas. Their collaborative approach to this book illustrates the way they "act as a unit" with other physicians in the perioperative care of our patients within a clinical approach that truly puts "patients first."

Christopher A. Troianos, MD, FASE
Chair, Anesthesiology Institute
Cleveland Clinic
Cleveland, OH, USA

Preface

With the establishment of the society of microcirculation in the 1980s, our understanding of microcirculation and tissue perfusion has fundamentally changed. The discovery of functions of endothelial glycocalyx and its essential role in maintaining the intact vascular barrier by Professors Curry and Michel has led to a new era in perioperative fluid management. The Starling Principle that was considered sine qua non for governing tissue perfusion since the 1920s and was written on a tablet of stone in medical textbooks was built on a false assumption of the structure of the blood vessels. Therefore, the Revised Startling Principle has replaced it, thanks to Drs. Curry and Michel's work in the field of microcirculation. The concept of liberal perioperative fluid management to compensate for the third space fluid loss was shown to increase the incidence of mortality and morbidity, especially in critically ill patients. The restrictive fluid management that properly should be named "normovolemic fluid management" has become an integral part of the enhanced recovery after surgery to improve the patients' perioperative outcomes. In this first edition of the *Perioperative Fluid Management* book, we tried our best to present the most comprehensive coverage of the most recent evidence-based medicine of fluid management written by world-renowned experts in the field. The book chapters cover different facets of fluid management, such as the history of intravenous fluid, goal-directed fluid management, balanced and unbalanced solutions, the dilemma with the use of hydroxyethyl starch solutions, the perioperative use of albumin, the effect of fluid overload on perioperative mortality and morbidity, and many more. We are honored to have the chapters for revised Starling Principle and endothelial glycocalyx written by the founding fathers of the modern science of microcirculation Drs. Curry and Michel who rewrote the story of the science of this field. Moreover, we added case scenarios for fluid management in different clinical settings to help guide the fluid management in a practical way.

We would like this book to benefit the understanding and fluid management of perioperative physicians.

At the end, we would like to express our gratitude to our colleagues who authored the book chapters for their efforts and hard work. In addition, we would like to thank Ms. Maureen Pierce our developmental editor and the Springer publishing team for all their help and support during the publishing process of this book.

Cleveland, OH

Ehab Farag, MD, FRCA
Andrea Kurz, MD

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Contributors

Maged Argalious, MD, MSc, MBA, MEd Anesthesiology Institute, Cleveland Clinic, Cleveland Clinic Lerner College of Medicine, Center for Anesthesiology Education, Cleveland, OH, USA

Kenton P. Arkill, PhD School of Medicine, University of Nottingham, Nottingham, UK

Biofisika Institute (CSIC UPV/EHU) and Research Centre for Experimental Marine Biology and Biotechnology, University of the Basque Country, Bilbao, Bizkaia, Spain

Harendra Arora, MD Department of Anesthesiology, University of North Carolina Hospitals, Chapel Hill, NC, USA

Hollmann D. Aya, MD Adult Critical Care Directorate, St. George's University Hospitals, NHS Foundation Trust and St George's University of London, London, UK

Verna L. Baughman, MD Department of Anesthesiology, University of Illinois, Chicago, IL, USA

Maurizio Cecconi, MD, FRCA, FICM, MD(UK) Anaesthesia and Adult Critical Care Directorate, St George's University Hospitals, NHS Foundation Trust and St George's University of London, London, UK

Andrew F. Cumpstey, MA (Cantab), BMBCh, MRCP Department of Anesthesia and Critical Care Medicine, University of Southampton, Southampton, UK

FitzRoy E. Curry, PhD Department of Physiology and Membrane Biology, and Biomedical Engineering, School of Medicine, University of California, Davis, Davis, CA, USA

John Danziger, MD, MPhil Division of Nephrology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Daniel De Backer, MD, PhD Department of Intensive Care, CHIREC Hospitals, Université Libre de Bruxelles, Brussels, Belgium

Jamil R. Dibu, MD Department of Neurocritical Care, Cerebrovascular Center, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA

Zeyd Y. Ebrahim, MD Department of General Anesthesiology, Anesthesiology Institute, Cleveland Clinic, Cleveland, OH, USA

Wael Ali Sakr Esa, MD, PhD Section Head Orthopedic Anesthesia, Department of General Anesthesia and Pain Management, Cleveland Clinic Lerner College of Medicine, Cleveland Clinic, Cleveland, OH, USA

Ehab Farag, MD, FRCA Professor of Anesthesiology, Cleveland Clinic Lerner College of Medicine, Director of Clinical Research, Staff Anesthesiologist, General Anesthesia and Outcomes Research, Cleveland Clinic, Cleveland, OH, USA

Elizabeth A.M. Frost, MBChB, DRCOG Department of Anesthesiology, Icahn Medical Center at Mount Sinai, New York, NY, USA

Michael P.W. Grocott, BSc, MBBS, MD, FRCA, FRCP, FFICM Department of Anesthesia and Critical Care Medicine, University of Southampton, Southampton, UK

Christiane S. Hartog, MD Department of Anesthesiology and Intensive Care Medicine and Center for Sepsis Control and Care, Jena University Hospital, Jena, Germany

Andrea Kurz, MD Professor of Anesthesiology, Cleveland Clinic Lerner College of Medicine, Chairman of General Anesthesia, Cleveland Clinic, Cleveland, OH, USA

Sheldon Magder, MD Department of Medicine and Physiology, Critical Care Division, McGill University Health Centre, Royal Victoria Hospital, Montreal, QC, Canada

Kamal Maheshwari, MD, MPH Acute Pain Management, Outcomes Research, Anesthesiology Institute, Cleveland Clinic, Cleveland, OH, USA

Edward M. Manno, MD Department of Neurocritical Care, Cerebrovascular Center, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA

Paul E. Marik, MBBCH, FCP(SA), FCCM, FCCP Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Eastern Virginia Medical School, Norfolk, VA, USA

C. Charles Michel, DPhil, BM.BCh, FRCP Department of Bioengineering, Imperial College, London, UK

Michael (Monty) G. Mythen, MBBS, MD, FRCA, FFICM, FCAI(Hon) Department of Critical Care, Anaesthesia and Perioperative Medicine, University College London, London, UK

William James Phillips, MD Department of Anesthesiology, Center for Critical Care Medicine, Cleveland Clinic, Cleveland, OH, USA

Konrad Reinhart, MD Department of Anesthesiology and Intensive Care Medicine and Center for Sepsis Control and Care, Jena University Hospital, Jena, Germany

Christopher Troianos, MD Anesthesia Institute, Cleveland Clinic, Cleveland, OH, USA

Thomas Edward Woodcock, MB, BS, MPhil Department of Critical Care, University Hospital Southampton, Southampton, UK

Part I
Fundamentals of Fluid Management

Chapter 1
A History of Fluid Management

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.

Keywords History • Blood • Fluid management • Bloodletting • Circulation • Fluid replacement • Cholera • Intravenous • Transfusion

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)

E.A.M. Frost, MBChB, DRCOG
Department of Anesthesiology, Icahn Medical Center at Mount Sinai,
New York, NY, USA
e-mail: elzfrost@aol.com; elizabeth.frost@mountsinai.org

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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 made. A theory of "channels" that carried air, water, and blood to the body was

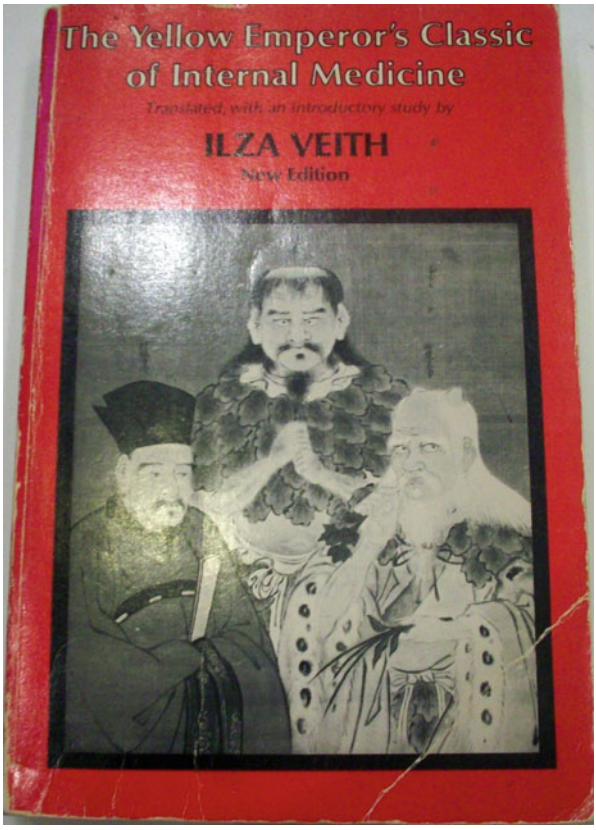

Fig. 1.1 *The Yellow Emperor's Classic of Internal Medicine*. On page 34, one reads, "When people lie down to rest, the blood flows back to the liver"

Fig. 1.2 The Edwin Smith Papyrus. The original belongs to the New York Academy of Medicine and is presently on loan to the Metropolitan Museum in New York

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 2nd 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.

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 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

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)

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 after having 3.75 l of blood removed from his body within a 10-h period as treatment for *cynanche trachealis* as noted by Drs. Craik and Dick (most likely a peritonsillar abscess) [18].

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, 19, 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

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 perorated 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

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

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

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 http://creativecommons.org/licenses/by/4.0/)

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].

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

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

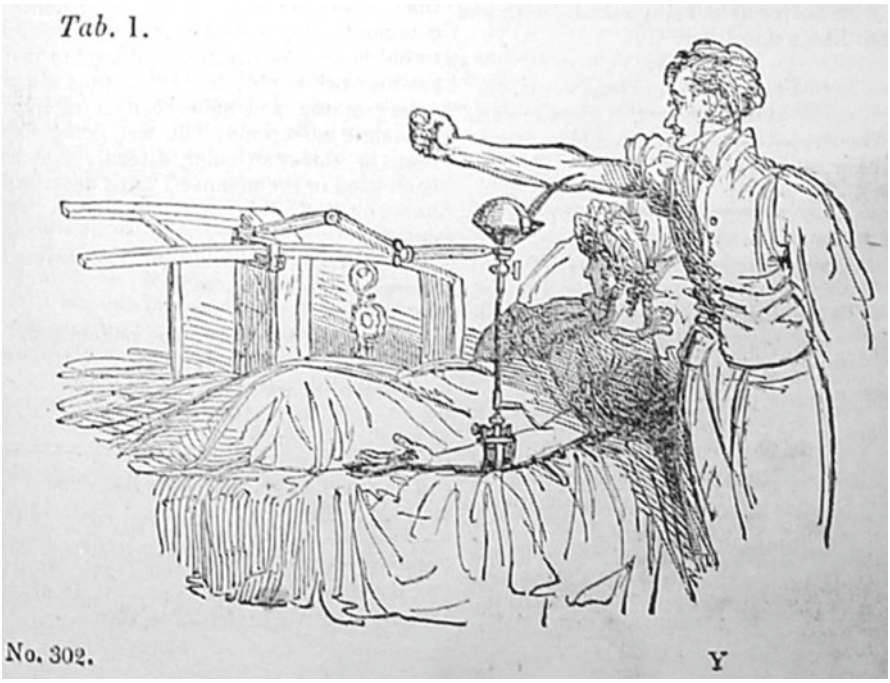

Fig. 1.8 Illustration of Blundell's human-to-human blood transfusion (Source: Blundell J. Observations on transfusion of blood. *Lancet*. Saturday, June 13, 1828; vol. II)

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, 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. "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. 1st to restore the blood to its natural specific gravity; 2nd 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].

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

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 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

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

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.

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 4 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 (1st 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 not 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 metabolic acidosis [118]. The colloid versus crystalloid debate continues [119]. Whereas, hydroxyethyl starch received a black box warning recently, newer studies suggest that may not have been entirely warranted [120].

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 is still not realized.

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Chapter 2
The Revised Starling Principle and Its Relevance to Perioperative Fluid Management

C. Charles Michel, Kenton P. Arkill, and FitzRoy E. Curry

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 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 being roughly matched by fluid gains from lymph. These differences in colloid osmotic pressure that determine blood-tissue fluid exchange are those across the ultrafilter in vessels walls, namely, the glycocalyx on the luminal surface of vascular endothelium. These differences are distinct from those between mean values of plasma and interstitial fluid since most macromolecules do not pass through the intact glycocalyx. Unlike transient changes, steady state fluid transport is nonlinear with changes in microvascular pressure. This nonlinearity predicts differing effects of the dilution of plasma protein depending on mean microvascular pressures, with increased transcapillary filtration when pressures are similar to plasma colloid osmotic pressure but negligible filtration at low pressures. Since pulmonary capillary pressures are low, monitoring plasma colloid osmotic pressure during large crystalloid infusions may be useful in averting pulmonary edema.

C.C. Michel, DPhil, BM.BCh, FRCP (✉)
Department of Bioengineering, Imperial College, South Kensington, London, UK
e-mail: c.c.michel@imperial.ac.uk

K.P. Arkill, PhD
School of Medicine, University of Nottingham, Nottingham, UK

Biofisika Institute (CSIC UPV/EHU) and Research Centre for Experimental Marine Biology and Biotechnology, University of the Basque Country, Bilbao, Bizkaia, Spain

F.E. Curry, PhD
Department of Physiology and Membrane Biology, and Biomedical Engineering, School of Medicine, University of California, Davis, Davis, CA, USA

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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 the microvessels 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 most 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 interstitial fluid flows through the tissue (e.g., lymph flowing through 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 colloid osmotic pressure is 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 filtration are very small but as pressure reaches Πp, 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 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.

List of Abbreviations

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
Pa, P_V	Arterial, venous pressures
Π	Colloid osmotic pressure
Π_P, Π_C, Π_I	Plasma, microvascular, interstitial (including sub-glycocalyx) colloid osmotic pressures.
Δ_P, Δ_Π	Hydrostatic and colloid osmotic pressure differences across glycocalyx
R_a, R_v	Pre-capillary and post-capillary resistance
σ	Membrane (osmotic) reflection coefficient
Σ	Summation
τ	Mean transit time

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 was 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 was 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 ultrafiltration of plasma through the capillary walls (see [5] and [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 micropuncture [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' 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, 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

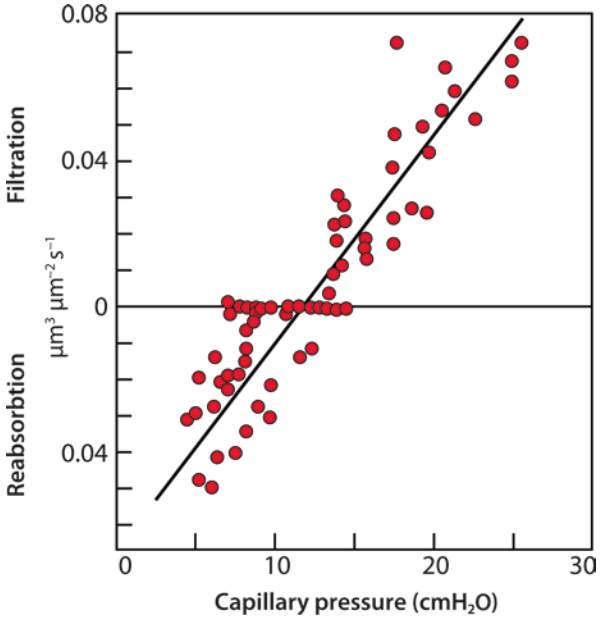

Fig. 2.1 The relationship between fluid movements through the walls of different capillaries in frog mesentery and the capillary's pressure as determined by Landis in 1927. Data replotted from original in *American Journal of Physiology* (Adapted with permission of the American Physiological Society, from Michel [29])

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 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 fluid exchange and permeability for the new edition of his monograph on capillaries [9].

After qualifying in medicine, Landis traveled 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 mmHg and in the venous limb a mean of 12 mmHg. At the halfway point at the tip of loop, its mean value was 25 mmHg. The colloid osmotic pressure of plasma of healthy volunteers is approximately 25 mmHg, 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].

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. 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

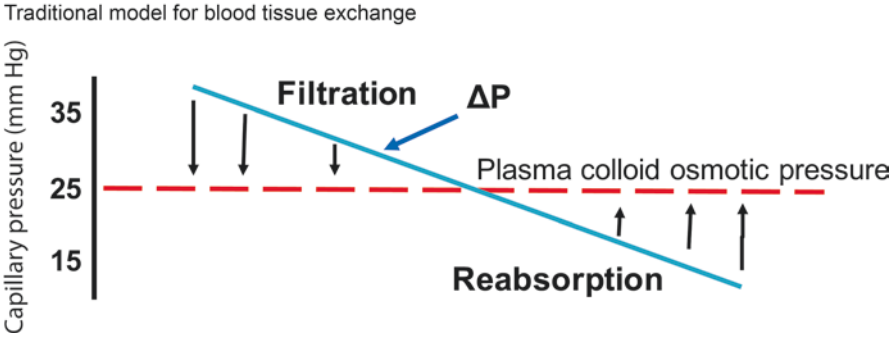

Fig. 2.2 Traditional model of blood-tissue fluid exchange where filtration is shown as occurring in the upstream section of an exchange vessel where ΔP is greater than the plasma colloid osmotic pressure, and absorption is downstream where ΔP is lower than the plasma colloid osmotic pressure. See also Fig.15a, a "diagram to forget"

fluid between the arterial and venous sides of the microcirculation and the tissues. Although their figures have been very widely quoted, the authors themselves were cautious about this; and Landis, 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, Pc in the capillaries of the toes of human subjects could be 100 mmHg 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, 16] 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 (see later section "A picture to forget").

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 coexisting arterial and venous pressures were spelt out clearly by Pappenheimer and Soto-Rivera in 1948 [18]. Arguing that if the net rate of loss or gain fluid by the blood flowing through a tissue is zero or 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. 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 precapillary resistance should equal the fall in pressure between the capillaries and the veins divided by the

postcapillary resistance. If P_a = arterial pressure, P_C = mean microvascular pressure, P_V = venous pressure, and R_a and R_V are the precapillary and postcapillary resistance of the circulation, then:

$$\frac{P_a - P_c}{R_a} = \frac{P_c - P_v}{R_v}$$

which may be rearranged as:

$$P_c = \frac{P_a + \left(\frac{R_a}{R_v}\right) P_v}{1 + \frac{R_a}{R_v}} \tag{2.2}$$

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 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 isogravimetric 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 isogravimetric conditions, blood flow increased linearly with reduction in the venous pressure. Arguing that in the isogravimetric 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 R_a/R_v from Eq. 2.2. Knowing the value of R_a/R_v, they could now calculate the values of P_c from the arterial and venous pressures when the limb was no longer in an isogravimetric 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 ~1–3 mmHg. It seemed that Starling's hypothesis had been emphatically confirmed.

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 [19]. 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 = molar concentration of solute in the solution) can only be measured across a perfectly semipermeable 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, ΔΠ, 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 ultrafiltration 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 semipermeable 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 ultrafilter 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 ultrafiltration 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 ultrafiltration 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, that is:

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

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 $\Sigma\sigma_i\Pi_i$ 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 [20] 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). Figure 2.3a shows an experiment where a single capillary has been perfused with two different Ringer's solutions [22]. 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 cmH_2O when the albumin concentration is high and at approximately 12 cmH_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 [21]. 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 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 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

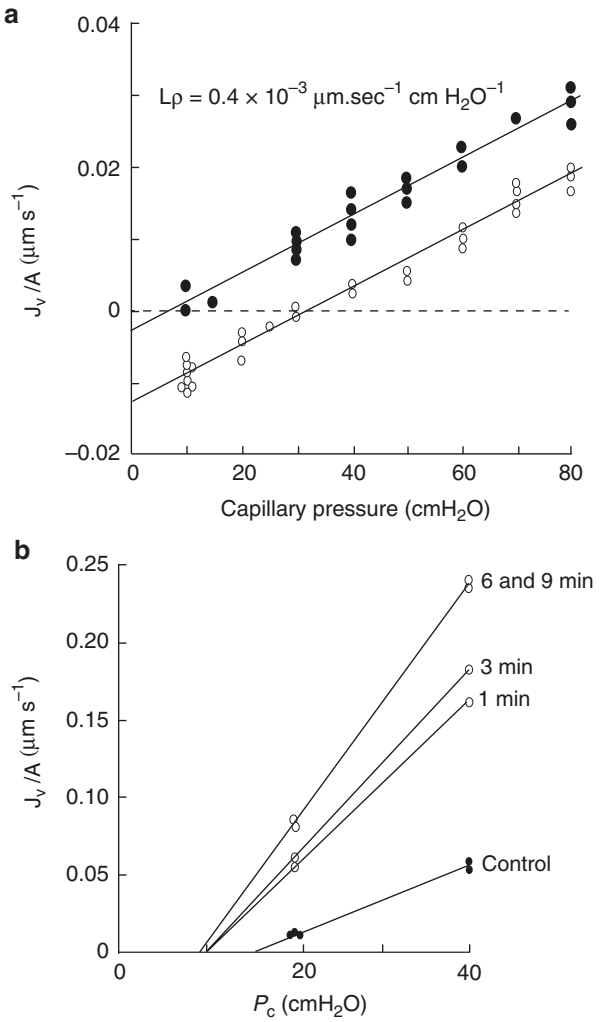

Fig. 2.3 Two experiments carried out on single perfused capillaries to illustrate the uses of the classical interpretation of Starling Principle when data are plotted in the way introduced by Landis. (**a**) The relation between fluid movements per unit area (J_V/A) and capillary pressure through the 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 from Michel [22]). (**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 and Kendall [21])

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 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 [23]. The values he measured were 2–7 mmHg 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 mmHg below atmospheric pressure. Although soon reproduced in other laboratories, the subatmospheric (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 [24] reported somewhat smaller (less negative) subatmospheric 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 subatmospheric pressures were artifacts of the measuring techniques was heightened when direct measurements using the servo-null micropipette technique, which had been developed to measure pressure in small blood vessels, yielded values of *Pi* around atmospheric pressure [25].

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 [26] 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 mmHg in subcutaneous tissues of rats and dogs. If the colloid osmotic pressure of the plasma was 25 mmHg, this indicated that the osmotic pressure difference available to move fluid from the tissues into the plasma was only 15 mmHg. At the same time, the subatmospheric values of P_I would add to the mean capillary

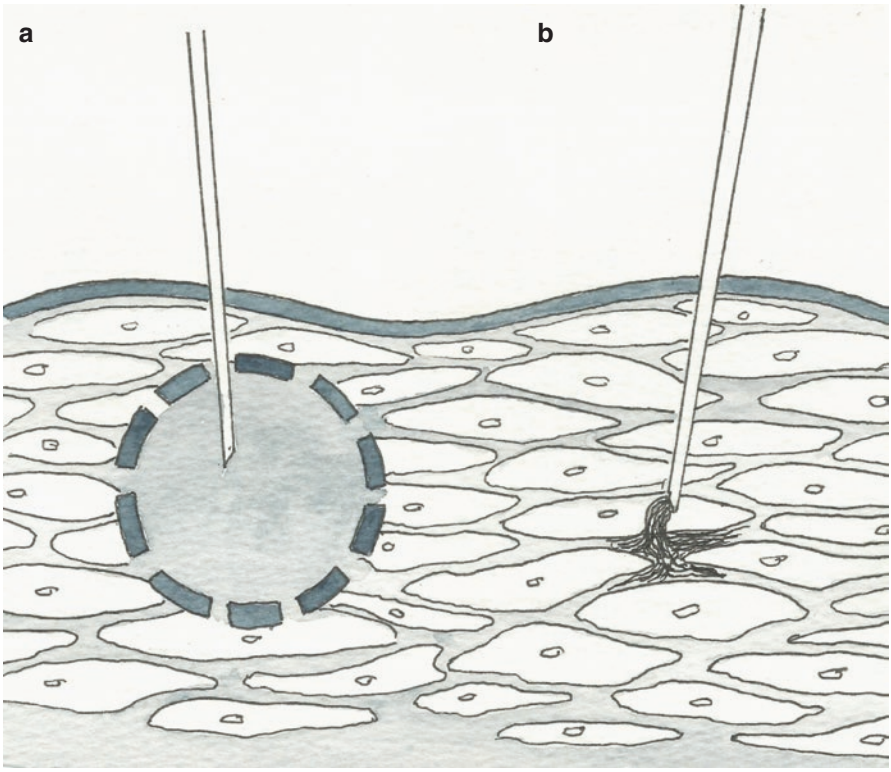

Fig. 2.4 Schematic diagram to illustrate the Guyton capsule (*a*) and the Aukland-Reed wick in needle (*b*) methods for measuring interstitial hydrostatic pressure and mean interstitial colloid osmotic pressure. Interstitial fluid hydrostatic and colloid osmotic pressures have also been measured in joint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

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 more than 10 mmHg. 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 [27–29]. The concept was reinforced by Chen

et al [28] 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 mmHg when Π_C was greater than 20 mmHg. 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 [30].

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 [31]. 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; that is:

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

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 [32]. 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 (nonfenestrated) 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. It involves a closer look at microvascular permeability and microvascular fluid exchange.

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

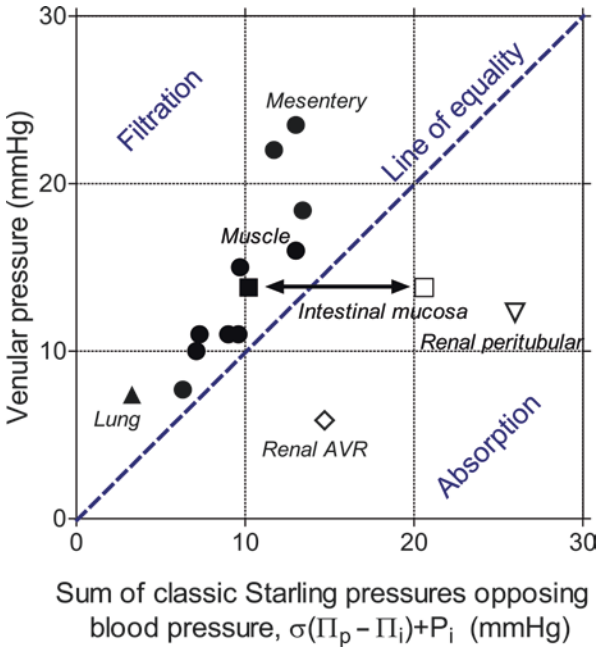

Fig. 2.5 The hydrostatic pressures in veins and venules of different tissues plotted against the sum of the pressures in those tissues that oppose fluid filtration. The Starling equilibrium or balance would be present if points lay on the line of equality. The points based on data from most tissues lie 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 nonabsorptive state (Reprinted with permission from Levick and Michel [32])

from the mean capillary hydrostatic pressure and plasma colloid osmotic pressure and the mean 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 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 and solute

molecules carried with the water (convection) 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. This is a steady state difference, its value is determined by the filtration rate (and its relation to the hydrostatic pressure difference) and the relative permeability of microvascular walls to water and macromolecules.

Box 2.2. Note on 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."

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. Because σ is high for macromolecules at most capillary walls, 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 ($\geq$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 ($1-\sigma$) multiplied by the

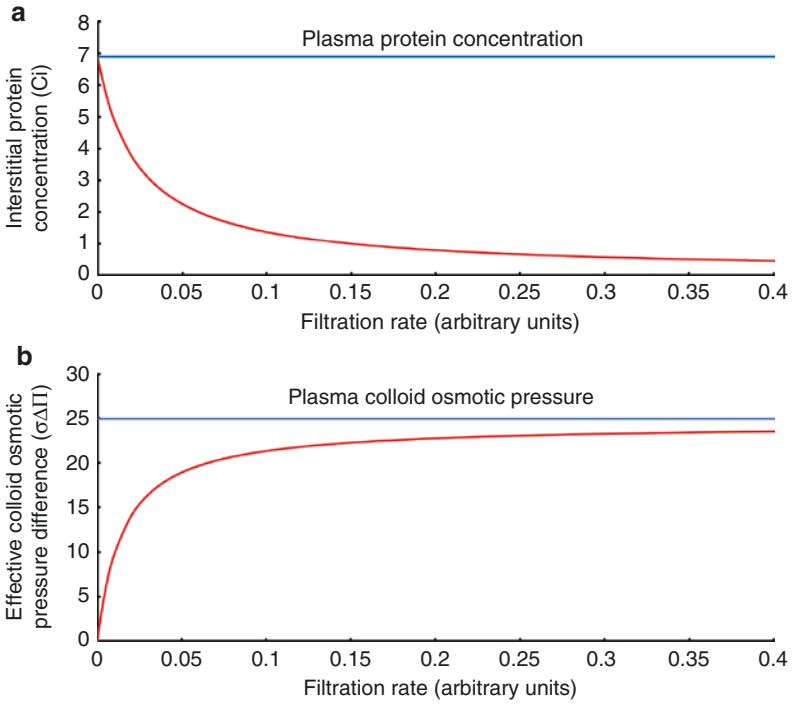

Fig. 2.6 The effects of changing filtration rate: (**a**) on steady state interstitial protein concentration and (**b**) the effective colloid osmotic pressure difference, $\sigma\Delta\Pi$, across microvascular walls. Note how $\sigma\Delta\Pi$ appears to reach a plateau at higher filtration rates

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. 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, $\sigma\Delta\Pi$, 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 [33].

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 [29]. It departed in one conspicuous way from the traditional interpretation of Starling's hypothesis

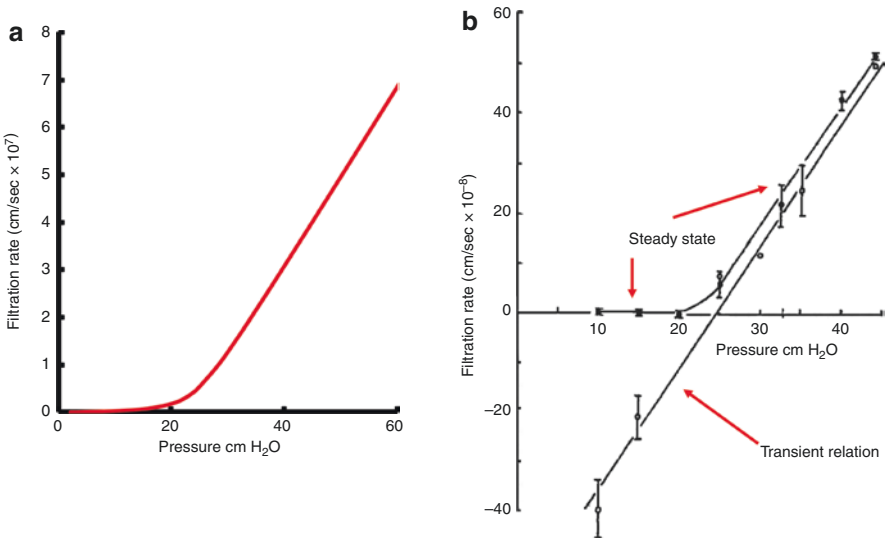

Fig. 2.7 (**a**) Steady state relations between fluid filtration rates and hydrostatic pressure difference across microvascular walls. At low pressures, steady state filtration increases only slightly with increments of pressure but as the pressure difference approaches the effective colloid osmotic 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 and Phillips [33])

(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 Principle where there is a steady filtration from the arterial side of the microcirculation and a steady fluid uptake on the venous side (Figs 2.2 and 2.15a).

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) [33, 34]. 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 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 out-

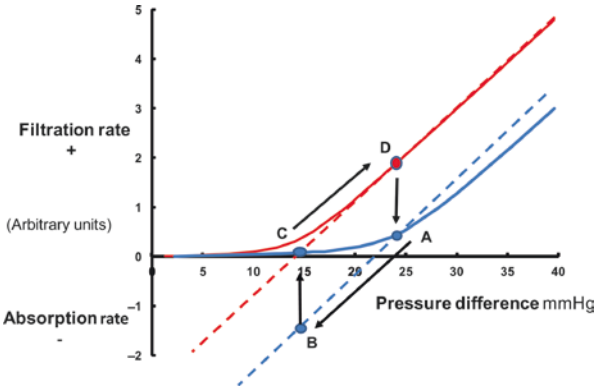

Fig. 2.8 Steady state relation between fluid movements and transcapillary hydrostatic pressure difference (*solid curve*) and transient changes in fluid movement following step changes in hydrostatic pressure. *Dashed lines* represent transient relations (see text)

side the exchange vessels reached its 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 perivascular 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 *Pi* when this was measured directly with a micropipette servo-null system just outside the microvessels [35]. The experiment showing the change from the linear transient relation between fluid exchange and capillary pressure and the nonlinear 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 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 2. Here the changes in $\sigma\Delta\Pi$ are accompanied by changes in P_I, which become less subatmospheric (less negative) to buffer rises in P_C and more negative when P_C falls. In skeletal muscle, fluid uptake from the tissue usually falls to zero within 30 min of a decrease of mean capillary pressure.

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 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 [36–38].

Steady fluid uptake also occurs into the high endothelial microvessels of lymph nodes [35, 39]. 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).

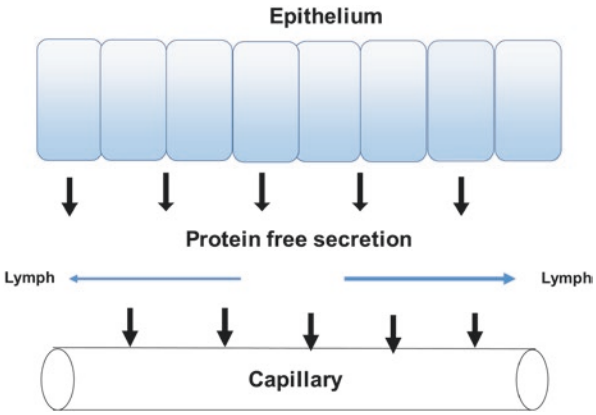

Fig. 2.9 Diagram to illustrate how the continuous uptake of fluid in capillaries of the intestine and renal cortex and medulla can be maintained by the secretion of protein-free fluid into the interstitial space from the nearby epithelium. In this way the protein concentration of the interstitial fluid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

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 ultrafiltering structures in microvascular walls. In experiments where the mean interstitial concentration of plasma proteins is maintained independently of composition of the capillary ultrafiltrate, differences between the mean interstitial colloid osmotic pressures and those on the tissue side of endothelial ultrafilter can even be present in the steady state [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 molecules of differing molecular size can be modeled 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, 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." 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 transendothelial 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).

Box 2.3. Aquaporin channels in endothelial cells
There is an additional pathway for water molecules that involves the aquaporin channels of the endothelial cell membranes of continuous (nonfenestrated) 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.

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 ultrafilter (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 is important to note that while the increase in $\sigma\Delta\Pi$ with the

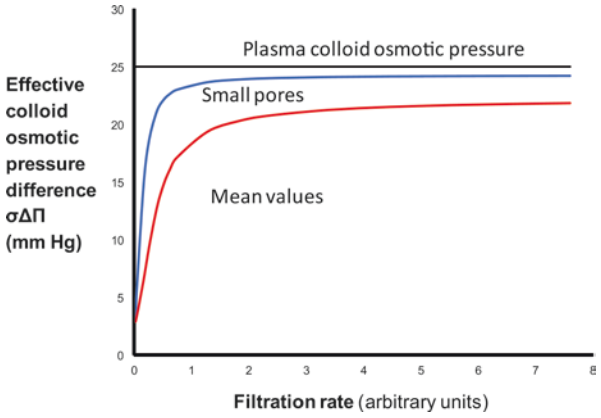

Fig. 2.10 Steady state relations between the effective osmotic pressure difference across skeletal muscle microvessels and fluid filtration rates comparing the mean values with those across the small pores (glycocalyx). Note how the effective osmotic pressure difference seen across the small pores (glycocalyx) 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

channels separated is only 4 mmHg (an improvement of 20 %) the important difference is that between the curves at higher filtrations rates and the plasma colloid osmotic pressure, which 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 [31] showed that it was most significant in those microvessels where the endothelia were continuous (nonfenestrated). For these vessels the same possible mechanism for separating the flows was suggested independently by Michel [6] and Weinbaum [40]. 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) [6]. The structural equivalent of the large pores are possibly very rare open intercellular clefts or vesicles including channels formed by fused vesicles that pass directly through the endothelium to its abluminal surface. Macromolecules passing through these 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

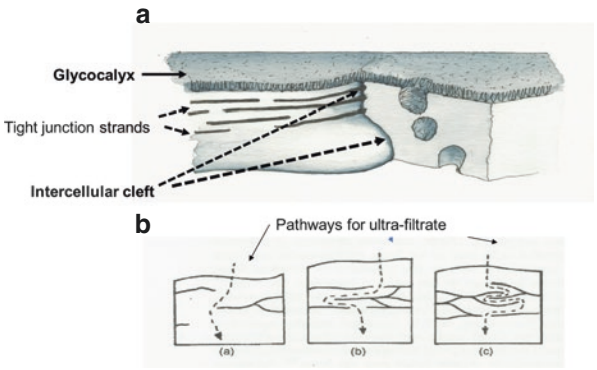

Fig. 2.11 Diagrams to illustrate the ultrastructure within an intercellular cleft between endothelial cells and the pathways through them for water and small hydrophilic solutes that have passed through the glycocalyx. (**a**) Part of the cell in the foreground has been removed to display the cleft interior. Note the junctional strands and the potential pathways through the breaks in them. (**b**) After flowing through the glycocalyx, which excludes macromolecules, the ultrafiltrate 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 [34])

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 [41].

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 [42] and later in rat mesenteric venules [43]. Figures 2.13 and 2.14 are taken from the paper by Adamson et al. [43] 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.

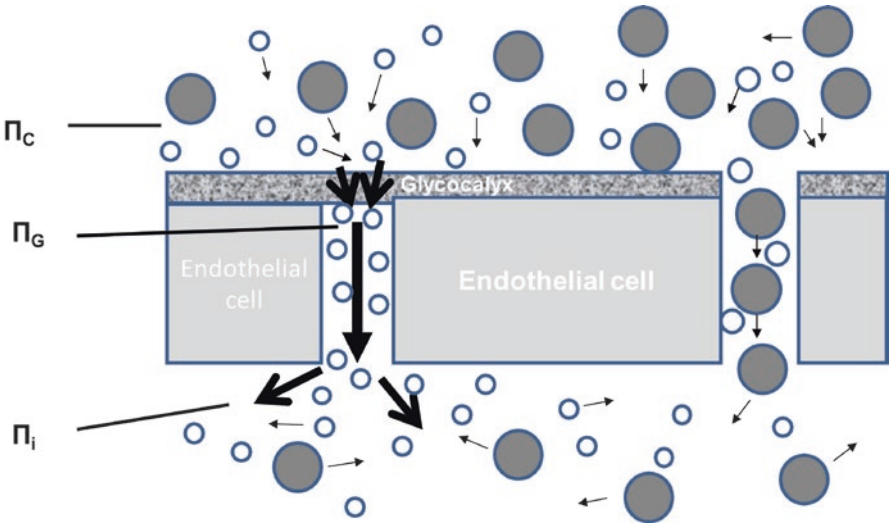

Fig. 2.12 A schematic diagram of fluid and protein exchange across walls of microvessels with continuous (nonfenestrated) endothelia. *Small open circles* represent water molecules; *large filled circles* represent protein molecules, with the plasma shown above the endothelium and the interstitial fluid 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 [41])

The superfusate was then changed to one that was identical to the perfusate in all respects except here the albumin was fluorescently labeled 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 redetermined. Under these conditions, one might 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.

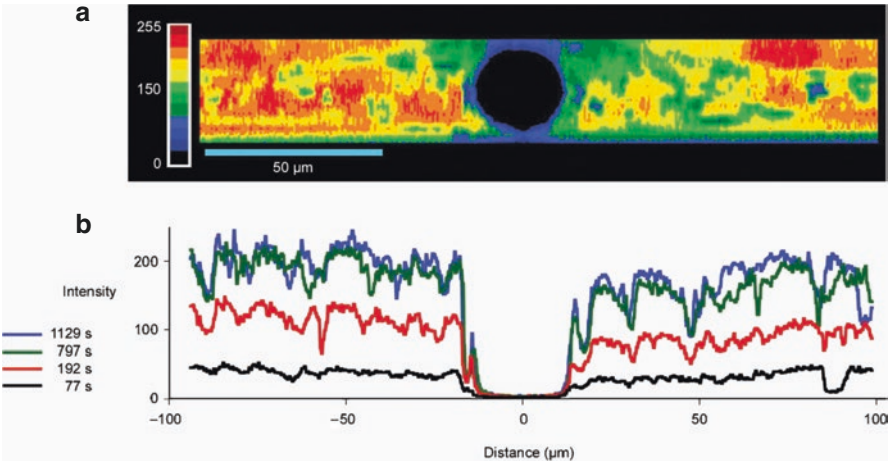

Fig. 2.13 Serum albumin concentration gradients around a venule in the rat mesentery at various times after fluorescently labeled albumin has been added to the superfusate. (**a**) Fluorescence image of a transverse section through the vessel and surrounding tissue. The vessel is perfused with an unlabeled 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 1 µ(mu)m of the vessel lumen (Reprinted with permission from Adamson et al. [43])

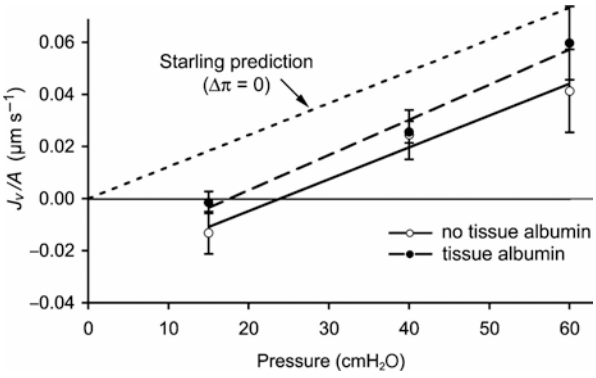

Fig. 2.14 Transient relations between filtration rates from a rat venule and microvascular pressure perfused with a solution containing serum albumin (50 mg/ml) when the superfusate washing the surface of the mesentery contains no albumin (*open circles*) and the same albumin concentration as that in 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 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 et al. [43])

This series of experiments also confirmed the validity of the steady state theory and like the earlier experiments of Michel and Phillips [33] 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 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 [44].

A Picture to Forget

A popular textbook diagram to illustrate the Starling's hypothesis depicts a linear fall in pressure along a capillary with its value at the arterial end in the range of 35 mmHg and with the venous end around 15 mmHg (Figs 2.2 and 2.15a). This sloping line crosses the horizontal line, which indicates the colloid osmotic pressure of the plasma of 25 mmHg. In the space between the lines when pressure is greater than 25 mmHg, 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 mmHg, the arrows point upward, indicating the uptake of fluid from the 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 [45]. Second, the increase in

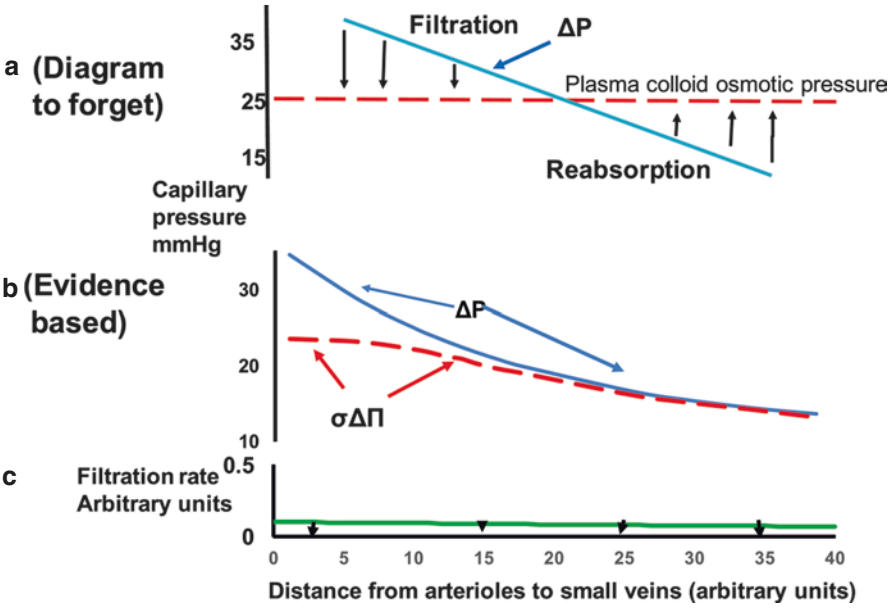

Fig. 2.15 (**a**) Version of the widely used textbook diagram to illustrate Starling's hypothesis with filtration occurring in the upstream section of an exchange vessel where $\Delta P >$ plasma colloid osmotic pressure, Π_p, and absorption downstream where $\Delta P < \Pi_p$. Interstitial colloid osmotic 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 mmHg 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

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 a-v 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 mmHg, it is soon reduced to 1 mmHg 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 mmHg, 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 [46]. 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 [39] and Knox and Pflug [47] demonstrated that the protein concentration of postnodal lymph was on average twice that in prenodal lymph. Both groups investigated lymph flows through the popliteal nodes of anesthetized dogs. Estimates of the prenodal and postnodal lymph flows by Adair et al [39] indicated that the doubling of protein concentration in the postnodal lymph was accompanied by a halving of lymph flow, indicating that half the prenodal flow was absorbed into the blood flowing through the node. Knox and Pflug [47] noted that the ratio of concentrations in the postnodal lymph to those in the prenodal lymph was the same for all proteins and independent of their absolute values. From this they concluded that higher concentrations in the postnodal 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 labeled albumin was injected directly into the prenodal lymph confirmed this interpretation [47]. 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 0.0025–0.004 ml min^{-1} $mmHg^{-1}$ 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 mmHg. Using these values, one calculates a net daily filtration of between 800 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 mmHg, 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 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 nonfasting 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 [31] drew attention 25 years ago. Following the argument implied in Fig. 2.15a, but subtracting mean ISF Π_I from Π_P, Bates et al [48] found that $\Delta P - \sigma\Delta\Pi$ exceeded the *venous* pressure in human forearm skeletal muscle by 4–5 mmHg. This meant the pressure difference driving filtration throughout the microvascular bed could be as high as 10 mmHg. Even if it were only 5 mmHg 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 nonlinear form (hockey stick shape) of the steady state relations between fluid filtration and microvascular pressure in guiding and interpreting the effects of intravenous fluid therapy. To illustrate this, we consider a question central to the controversy of whether intravenous infusion of solutions containing colloids are considerably more effective in expanding circulating plasma volume than infusion of crystalloid solutions and compare the predictions of the classical interpretation of Starling Principle with more recent views.

Consider first a healthy volunteer in whom P_C has a mean value of 22 mmHg allowing only a very low level of filtration from plasma into the tissues. If a solution with the same colloidal osmotic pressure as the subject's plasma were now infused into the circulation, it should increase the plasma volume. If P_C remained unchanged, according to both the classical and the revised interpretations of Starling Principle, the increase in plasma volume would approximate closely to the volume of colloid solution infused and decline slowly as other systems responded to the increase in plasma volume, leading to diuresis and increased permeability to plasma proteins in response to natriuretic peptides [49, 50]. Only if the increase in blood volume led to a sufficient increase in venous return and cardiac output to raise mean P_C, either through an uncompensated rise in mean arterial pressure or through reflex, reduction of the pre- to postcapillary resistance to hold the mean arterial pressure constant, should fluid movement from plasma into the tissues increase. To illustrate the effect of a reduction in R_a/R_v, let $P_a = 100$ mmHg, $P_V = 10$ mmHg, and initially $R_a/R_v = 5{:}1$, then from Eq. 2.2, $P_C = 25$ mmHg; if now R_a/R_v is reduced from 5:1 to 3:1, P_C now is equal to 32.5 mmHg. Both the classical and the revised interpretations of Starling Principle would then predict that an increase in P_C of 7 mmHg would lead to a significant increase in filtration rate.

Infusion of a purely crystalloid solution, however, dilutes the plasma proteins, reducing plasma colloidal osmotic pressure and immediately increasing filtration from plasma to tissues. The classical interpretation of Starling Principle predicts that filtration rates will increase with progressive dilution of the plasma proteins at constant P_C and would be further increased if P_C were to rise. The rate at which blood volume expands is the difference between the rate of infusion and the rate of filtration from plasma to tissues plus urine flow. When the infusion ends, fluid filtration should continue until most of the infused crystalloid solution has been distributed between the plasma and the ISF so that the dilution of the ISF proteins and concentration of the plasma proteins balance the mean hydrostatic pressures across microvascular walls.

When mean capillary pressure is in the normal range, the predictions of the revised Starling Principle would be quite similar to this classical interpretation. The blue curve in Fig. 2.16a shows the steady state relations between filtration rate and ΔP before the infusion of crystalloid solution when plasma protein concentration is in the normal range and plasma colloid osmotic pressure was 25 mmHg. The red curve shows the steady state relations after a crystalloid solution has been infused into the circulation to dilute the plasma proteins sufficiently to reduce the plasma colloid osmotic pressure to 15 mmHg. If the subject were a healthy volunteer with a mean capillary pressure in his skeletal muscles of approximately 22 mmHg, his steady state fluid exchange before the infusion is seen as point A. With the infusion of crystalloid at constant P_C, both classical and revised interpretations of Starling Principle would predict that filtration into the tissue is stimulated along the vertical line to point B, when the plasma colloid osmotic pressure is reduced to 15 mmHg.

Differences between classical and revised interpretations, however, are expected if we consider the intravenous infusion of crystalloid solutions in patients where the

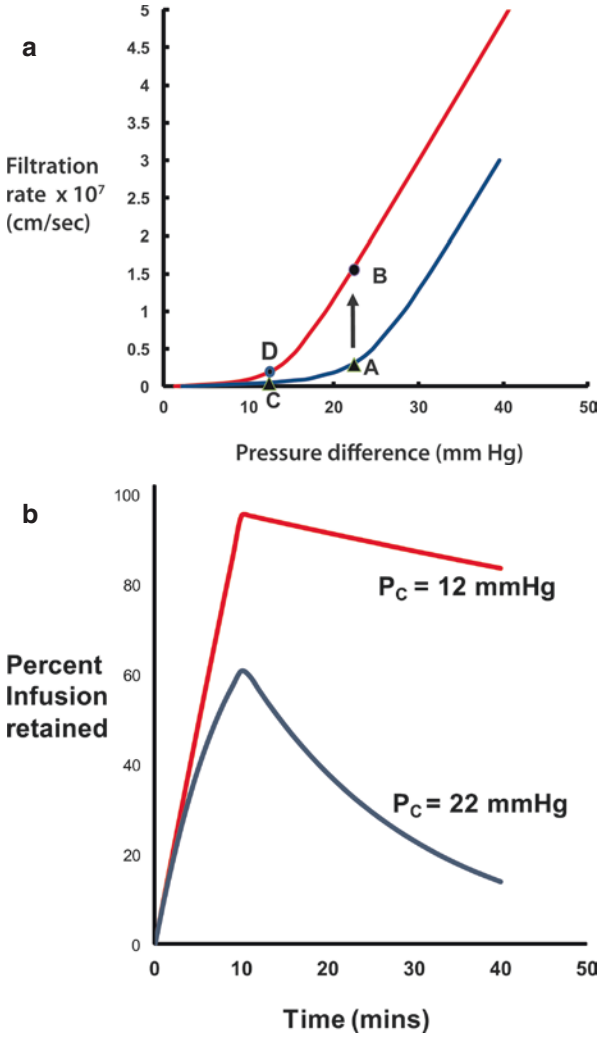

Fig. 2.16 (**a**) Steady state relations between fluid filtration and mean microvascular pressure when plasma osmotic pressure is in the normal range (*blue curve*) and after dilution of the plasma proteins by crystalloid infusions to reduce colloid osmotic pressure by 10 mmHg (*red curve*). Point A represents the position in a healthy subject at rest with average mean microvascular pressure of 22 mmHg and point B shows the filtration rate at the same microvascular pressure when the plasma proteins have been diluted by crystalloids. Point C represents steady state filtration rate in a tissue such as muscle when the microvascular pressure has been reduced by intense vasoconstriction following blood loss. Whereas dilution of the plasma proteins by crystalloid infusion leads to a substantial increase in fluid filtration at normal P_C, when P_C in reduced by intense vasoconstriction (point C), dilution of the plasma proteins raises filtration rate only marginally to point D. Only when the plasma colloid osmotic pressure has been reduced below the reduced P_C are significant increases in fluid filtration seen. (**b**) 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

mean capillary pressure is below $\sigma\Delta\Pi$. For example, after losing 20 % of the blood volume, mean P_C in muscle would be reduced considerably as a result of reduced circulating volume and by arteriolar vasoconstriction (increasing R_a/R_v) to compensate for this. The classical interpretation would predict that at low P_C fluid uptake from the tissues would expand the plasma volume until the dilution of the plasma proteins reduces the plasma colloid osmotic pressure to a level comparable with that of mean P_C. This compensatory mechanism would be compromised by crystalloid infusion and if any increase in the circulating fluid volume did occur it would be short lived. From this one would conclude that attempts to correct a reduced blood volume by infusion of crystalloid solutions should be avoided, for their effects will be at the best transient and at the worst counterproductive.

The revised interpretation would also predict that the intense peripheral vasoconstriction with a large fall in mean P_C would lead to a brisk uptake of fluid from the tissues and be seen as a fall in hematocrit. The rate of fluid uptake, however, would diminish and after 30 min or so revert to a very low level of filtration as fluid exchange approached a new steady state. Here, when P_C is well below $\sigma\Delta\Pi$, J_V/A lies on the flat portion of the steady state curve, becoming almost insensitive to changes in plasma colloid osmotic pressure (point C in Fig. 2.16a). Infusion of crystalloid solution now leads to only very small increases in filtration rate until $\sigma\Delta\Pi$ is reduced below P_C (up to point D in Fig. 2.16a). While the classical interpretation of the Starling Principle suggests that crystalloid infusions prevent the compensatory responses to a reduced circulating volume, the revised interpretation predicts that when P_C is low, crystalloid infusions should be retained in the circulation almost as effectively as colloid solutions. This is illustrated in Fig. 2.16b.

This consequence of the revised interpretation may account for the observation that crystalloid solutions appear to be far more effective in increasing a patient's plasma volume in the operating room or after trauma than they are in a healthy volunteer in the experimental laboratory [51]. Based on the classical interpretation, animal models, and the relative volumes of blood and ISF, it has been believed that to achieve equal increases in plasma volume by intravenous infusion, the volume of crystalloid solutions required is three times greater than that of colloid solutions (e.g., [52]). Anecdotal reports that crystalloid infusions are more effective than this in clinical situations has been supported by a series of trials, which have found that in patients in intensive care, similar hemodynamic measures can be achieved by volumes of crystalloid solutions only slightly greater than those of colloids (e.g., [53]; for review see [54]). In many, if not most, of these patients, mean P_C is low as a result of reduced cardiac output and/or intense arteriolar constriction so that fluid filtration from plasma to tissue is on the flat portion of the curve relating J_V and P_C. By underlining the importance of P_C in determining both the filtration rate and the effective osmotic pressure difference opposing filtration, the revised interpretation provides a physiological basis for the more effective volume-restoring properties of crystalloid solutions here.

Although changes in circulating plasma volume are shown in Fig. 2.16, it should be remembered that its near constant value is predicted on the assumption that all

microvessels have the same permeability properties to fluid and macromolecules as those found in skeletal muscle. This, of course, is not the case. Under "normal" circumstances, fluid and macromolecules are continually being lost from the circulation at different rates in different tissues. Plasma volume is kept approximately constant by the return of fluid to the circulation by its absorption from dilute lymph in the capillaries of the peripheral lymph nodes [39, 47] and by the return of more concentrated lymph via the thoracic and right lymphatic ducts. Superimposed on classical transcapillary fluid exchange are the addition of fluids to the circulation by absorption from the gastrointestinal tract (following ingestion) and losses of fluid through the kidneys.

Because the plasma volume is determined by these different rates of fluid entry and fluid loss, its constancy is only approximate in healthy individuals. Deviations in its value that are large enough to alter venous return (and hence cardiac output) are detected by the low pressure and high pressure baroreceptors and corrected rapidly by cardiovascular reflexes. More complete adjustments are achieved more slowly by fluid absorption and renal excretion. When blood volume is reduced, the reflex vasoconstriction in tissues such as skeletal muscle increases in R_a/R_v and not only raises the mean arterial pressure promoting perfusion of the heart and brain but also reduces mean microvascular pressures, facilitating a short period of fluid uptake from the tissue that is followed by a minimal rate of fluid loss. The immediate response to expansion of the blood volume is vasodilatation and, if central venous pressure is raised, release of natriuretic peptides, which not only increase urine flow but also raises hydraulic and macromolecular permeability of microvessels in different tissues [49, 50, 55–57]. These responses increase fluid filtration, for not only will vasodilatation involving a reduction of R_a/R_v increase mean microvascular pressures but increased microvascular permeability steepens all regions of the steady state curves relating fluid filtration to microvascular pressure differences.

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. This has already been illustrated by the differing effects of crystalloid infusions on filtration rates when average P_C in tissues such as muscle approximates to plasma colloid osmotic pressure and when P_C is 5 mmHg or more lower than this. At present, there is no easy way for the clinician to know the value of the mean P_C in major components of the systemic circulation.

The clinician may, however, be guided by the revised interpretation when considering the effects of fluid therapy on the pulmonary circulation. The greatest risk from overtransfusion is pulmonary edema. The lungs of healthy individuals are protected from edema by the low microvascular pressures in pulmonary capillaries (7–10 mmHg) and 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, the interstitial hydrostatic pressure in lungs lies normally in the range of −5 to −10 mmHg (subatmospheric) 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 mmHg or so below its upward inflection (similar to point C in Fig. 2.16a). 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 12 mmHg.

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 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 volumes of the red cells and plasma, respectively, in the circulation, it seems reasonable to say:

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

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

If H_1 is the hematocrit of a sample of blood taken from a patient before a procedure and H_2 is its value 40 min after infusion of 500 ml of a crystalloid solution, then 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:

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

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 300 ml of the 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 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. If the initial plasma volume were 3 l, the measured change of hematocrit would suggest an increase in plasma volume of 539 ml, 39 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} falling between 0.88 and 0.94 for most healthy (and nonpregnant) adults. In pregnancy (where maternal blood volume is expanded) the ratio falls and in the new born it may be as low as 0.8 [58]. 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.

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:

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

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.

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 ultrafiltering structure within microvascular walls. This is the glycocalyx at the luminal surface of endothelium. In vessels with continuous (nonfenestrated) 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.

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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 1.

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:

$$J_S = J_V(1-\sigma)C(x) + D\left(-\frac{dC(x)}{dx}\right) \tag{2.1A}$$

where $C(x)$ is the solute concentration at x.

Rearranging Eq. 2.1A and integrating leads to:

$$\begin{aligned} \frac{dC(x)}{dx} &= \frac{J_V(1-\sigma)}{D}\cdot C(x) - \frac{J_S}{D}, \\ C(x) &= \frac{J_S}{J_V(1-\sigma)} + A\cdot\exp\left[\frac{J_V(1-\sigma)\cdot x}{D}\right] \end{aligned} \tag{2.2A}$$

where A is a constant.

When $x = 0$, $C(x) = C_1$ so that:

$$A = C_1 - \frac{J_s}{J_V(1-\sigma)}$$

When $x = \Delta$, $C(x) = C_2$ and:

$$\begin{aligned} C_2 = \frac{J_S}{J_V(1-\sigma)} + \left[C_1 - \frac{J_S}{J_V(1-\sigma)}\right]\exp\left(\frac{J_V(1-\sigma)\cdot\Delta}{D}\right) = \frac{J_S}{J_V(1-\sigma)} \\ + \left[C_1 - \frac{J_S}{J_V(1-\sigma)}\right]e^{Pe} \end{aligned} \tag{2.3A}$$

where $J_V(1-\sigma)\bullet\Delta/D$ = Péclet number = Pe. The Péclet number can be thought of as the ratio of the solute velocity by convection to its velocity by diffusion. The ratio D/Δ is the diffusional permeability of the solute across the membrane.

Rearranging Eq. 2.3A leads to:

$$\frac{J_S}{J_V(1-\sigma)} = \frac{C_1 - C_2e^{-Pe}}{\left(1-e^{-Pe}\right)} \tag{2.4A}$$

When steady state concentrations are established across the membrane, $J_S/J_V = C_2$ so that Eq. 2.4A becomes:

$$\frac{C_2}{(1-\sigma)} = \frac{C_1 - C_2e^{-Pe}}{\left(1-e^{-Pe}\right)} \tag{2.5A}$$

Further manipulation leads to:

$$C_2 = C_1 \frac{(1-\sigma)}{(1-\sigma e^{-Pe})} \tag{2.6A}$$

And the concentration difference across the membrane is:

$$C_1 - C_2 = C_1 \sigma \frac{(1-e^{-Pe})}{(1-\sigma e^{-Pe})} \tag{2.7A}$$

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:

$$\Delta\Pi = \Pi_1 \sigma \frac{(1-e^{-Pe})}{(1-\sigma e^{-Pe})} \tag{2.8A}$$

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:

$$J_V = L_P \left[\Delta P - \sigma^2 \Pi_P \frac{(1-e^{-Pe})}{(1-\sigma e^{-Pe})} \right] \tag{2.9A}$$

Equation 2.9A 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:

$$\Delta P = \frac{J_V}{L_P} + \sigma^2 \Pi_P \frac{(1-e^{-Pe})}{(1-\sigma e^{-Pe})} \tag{2.10A}$$

When appropriate values for the permeability coefficients are substituted into Eq. 2.10A, nonlinear curves similar to those shown in Figs. 2.7, 2.8, and 2.15a can be constructed. It is important to use Eq. 2.10A not 2.9A for reconstructing the curved steady state relation, since J_V appears on both the left and right hand sides (in *Pe*) of Eq. 2.9A. Equations 2.9A and 2.10A are approximations because the assumption made in Eq. 2.8A 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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Chapter 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

FitzRoy E. Curry, Kenton P. Arkill, and C. Charles Michel

Abstract The glycocalyx establishes the osmotic pressure difference of the plasma proteins across the vascular wall and plays a major role in determining 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 explains why 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 must be carefully evaluated. It provides a detailed analysis of two modern approaches to measure glycocalyx function in

F.E. Curry, PhD (✉)
Department of Physiology and Membrane Biology, and Biomedical Engineering, School of Medicine, University of California, Davis, Davis, CA, USA
e-mail: fecurry@ucdavis.edu

K.P. Arkill, PhD
School of Medicine, University of Nottingham, Nottingham, UK

Biofisika Institute (CSIC UPV/EHU) and Research Centre for Experimental Marine Biology and Biotechnology, University of the Basque Country, Bilbao, Bizkaia, Spain

C.C. Michel, DPhil, BM.BCh, FRCP
Department of Bioengineering, Imperial College, South Kensington, London, UK

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clinical settings: (1) measurement of glycocalyx volume as a difference between the distribution volumes of red cells and macromolecular tracers; and (2) direct visualization of changes in the penetration of red cells into the cell-free layer at the walls of sublingual microvessels. Method 1 overestimates glycocalyx volume because it assumes tracer concentrations in the glycocalyx and plasma are the same, and also assumes large vessel hematocrit provides an unbiased measure of plasma volume in the whole circulation. Method 2 appears to characterize some microvascular dysfunction, but 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 reevaluate 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.

Keywords Glycocalyx • Glycocalyx structure-function • Glycocalyx volume • 3D glycocalyx reconstruction • Sidestream dark field imaging • Revised Starling Principle • Glycocalyx composition • Electron microscopy of glycocalyx

Key Points

1. The glycocalyx establishes the osmotic pressure difference of the plasma proteins across the vascular wall and plays a major role in determining 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 fibrous networks 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 avoidance of conditions of both hypovolemia and hypervolemia. 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.

4. Measurement of glycocalyx volume as a difference between the distribution volumes of red cells and macromolecular tracers such as dextran and albumin, while simple in principle, always overestimates the volume of plasma within the glycocalyx. This is because tracer concentrations measured in plasma are never representative of those within the glycocalyx and large vessel hematocrit is not representative of the volume of plasma and red cells in the circulating blood in organs with varying vascular transit times.
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 appears to be increased penetration of red cells toward the vessel wall in microvessels up to 50 micron 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 perioperative fluid therapy.

Introduction

The endothelial glycocalyx constitutes the first contact surface between blood and tissue and 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 molecule movement through vascular endothelium, senses the magnitude of local blood flow and regulates local nitric oxide production, 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 difference between circulating blood and the body tissue, and the consequences of this for fluid therapies is described in the accompanying chapter on the Revised Starling Principle (see Chap. 2).

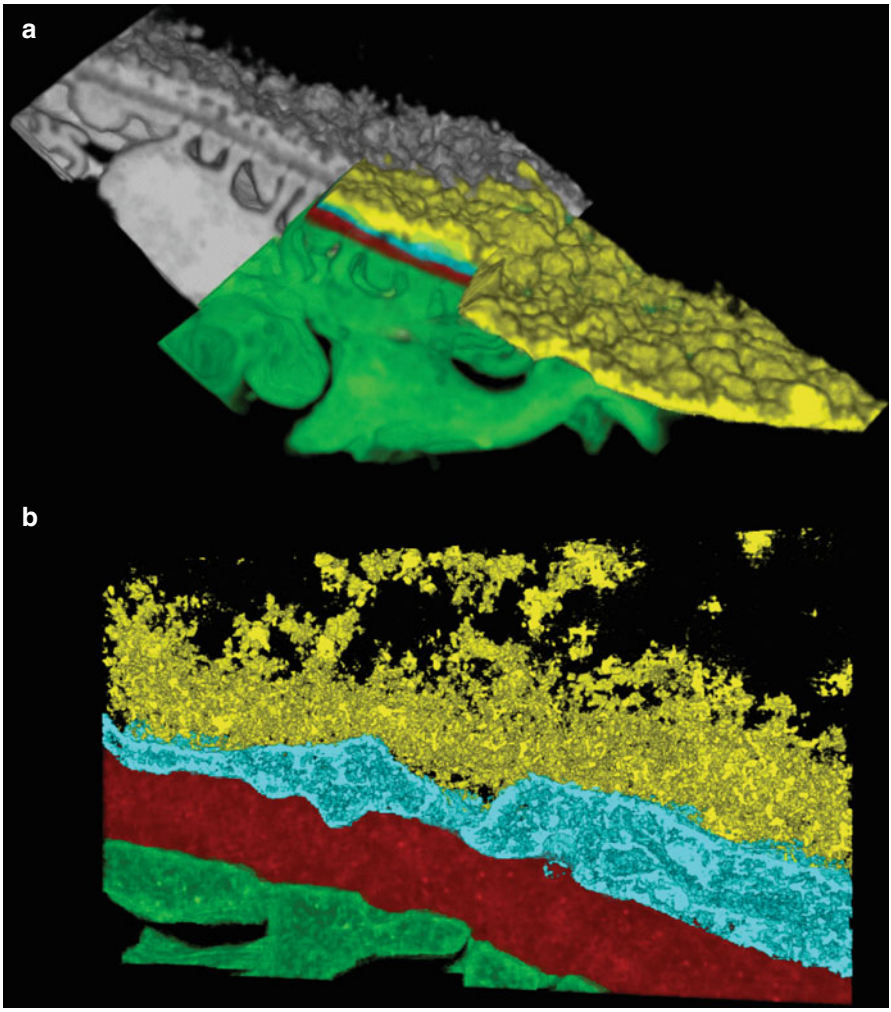


Fig. 3.1 The endothelial glycocalyx of a renal glomerular filtration capillary. The figure with parts of the glycocalyx (*yellow*), endothelium (*blue*), glomerular basement membrane (*red*), and podocyte foot processes (*green*) colored for emphasis is adapted with permission from Arkill et al. [16]. The glycocalyx was stained with the LaDy GAGa technique. The original data were: (**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. For details of the glycocalyx staining and 3D scanning electron microscopy of the glycocalyx, see text: "Background: Imaging the Glycocalyx: More Detailed Technical Issues."

In this chapter, the focus is on the evolving understanding of the glycocalyx as a three-dimensional (3D) 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 nonfenestrated microvessels fixed under a variety of conditions and using both conventional as well as newer ways to stain glycocalyx components [16, 17] (see later sections: "The Glycocalyx as a Three-Dimensional Layered Structure in Microvessels" and "Background: Imaging the Glycocalyx: More Detailed Technical Issues"). An evaluation of such a 3D structure is important because:

1. The regulation of the different physiological functions of the glycocalyx described earlier (e.g., permeability barrier versus lubrication layer for red cell movement through microvessels) depends on 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 requires knowledge of the heterogeneity of the glycocalyx and its internal organization.
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 the glycocalyx is a relatively uniform structure.

We will discuss these topics, 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 (Fig. 3.2) [3, 18]. 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

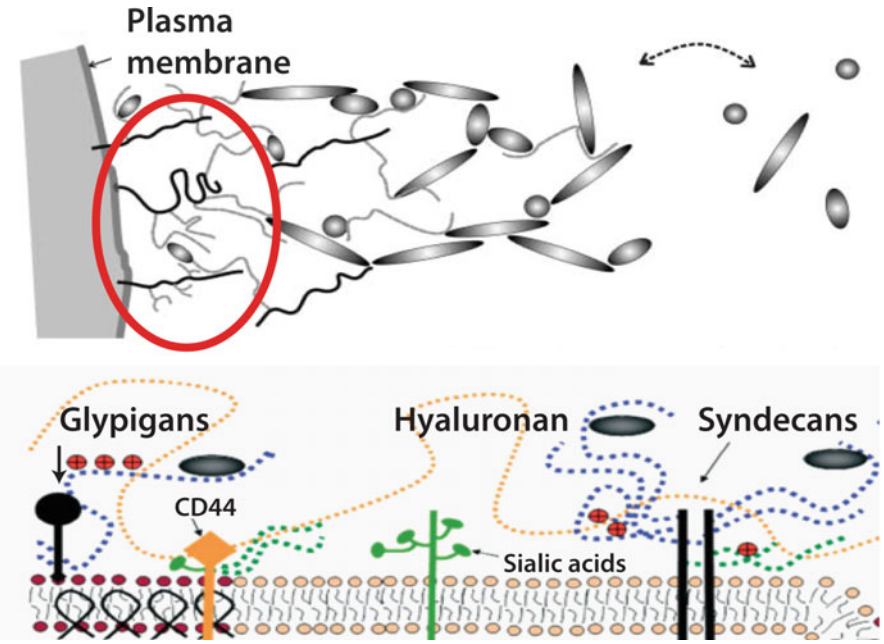


Fig. 3.2 One of the earliest attempts to illustrate the endothelial glycocalyx as a complex three-dimensional structure is shown in the *top panel*. The hypothetical model emphasizes the presence of an inner region (*highlighted in red*) consisting of glycoproteins and proteoglycans associated with the 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. Hyaluronic acid a long disaccharide polymer forms part of the scaffold for the outer layer, which also includes adsorbed plasma proteins (*shown as circles or elongated discs*) and solubilized glycosaminoglycans (*shown as linear fragments*). 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 form part of the lubrication layer for red cells (*Top panel* reproduced with permission from Pries et al. [3]. *Lower panel* adapted with permission from Tarbell and Pahakis [18])

negative charge, and other electrostatic and weak chemical interactions with plasma constituents including hyaluronic acid, plasma proteins, and small electrolytes. 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. These include:

- *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 (CS) [20]. Syndecans reside close to the endothelial membrane with cytoplasmic tails associated with the cytoskeleton. These attachments are assumed to play a role in the organization of the glycocalyx [21, 22]. Because the molecular weights of

GAGs and core proteins suggest molecular lengths from the endothelial surface of the order of 100 nm, it is likely that syndecans form part of the inner layers of the glycocalyx.

- *The glypicans*: Glypican-1(64 kD), a member of the Glypigan family of core proteins, is expressed on ECs. Glypican-1 is bound directly to the plasma membrane through a C-terminal glycosylphosphatidylinositol (GPI) anchor [23]. The GPI anchor localizes this proteoglycan to the specialized membrane domains called lipid rafts that include the endothelial surface caveolae. The GAG attachment sites in Glypigan-1 are exclusively substituted with heparan sulfate.
- *Hyaluronic acid*: In contrast to these core proteins, hyaluronic acid (HA) is a much longer disaccharide polymer, of the order of 1,000–10,000 KD (lengths can be of the order of several microns), synthesized on the cell surface and not covalently attached to a core protein [24]. HA associates with the glycocalyx through its interaction with surface receptors, such as the transmembrane glycoprotein CD44, and CS chains [25, 26]. Because of its large molecular dimension, HA side chains can extend well beyond the core proteins and thereby form part of the scaffold for the glycocalyx, HA is not sulfated but obtains its negative fixed charge density from carboxyl groups that endow it with exceptional hydration properties.
- *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 [27]). 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 below).
- *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, 28]. 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 [29], diabetes [30], and exposure to a range of infections and inflammatory agents including tumor necrosis factor-α(alpha), cytokines, proteases, and other enzymes including heparanase (see [9, 11, 31]). Most current analytical techniques to measure circulating glycocalyx components rely mainly on enzyme-linked immunosorbent-based assays (ELISA), 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 sulfate (tenfold from a baseline of 5 mg/ml) in patients undergoing major vascular surgery [29] and increased syndecan-1 (27.1–110 ng/ml) and HA (16.8–35.0 ng/ml)

in dialysis patients [32]. Similarly, increased levels of plasma HA in type 1 diabetes are associated with increased circulating level of hyaluronidase (170 U/ml to 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 discussed 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 [33]. These authors reported 23-fold increases in the amount of HS fragments after lung injury.

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, 34]. In both animal models and clinical studies, direct restoration of glycocalyx components to circulating plasma (e.g., HA and CS [25]) or the infusion of glycosaminoglycan precursors, are reported to restore some function [35]. However, the mechanisms to stimulate synthesis and reassemble the glycocalyx remain to be investigated in much more detail.

New insight into the balance between stabilization of the glycocalyx and its degradation comes from the observation that albumin, previously understood as an essential structural component of the glycocalyx, is part of a homeostatic mechanism that regulates glycocalyx degradation. Specifically, Zeng and colleagues [36] demonstrated that heparan sulfate (HS), chondroitin sulfate (CS), 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 anti-inflammatory 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. These observations established that albumin binds S1P and carries it to the endothelium the normal circulation albumin carries 40 % of the circulating S1P. Apolipoprotein M in high-density lipoproteins carries most of the remainder [37]. The action of S1P to preserve of glycocalyx components was shown to involve suppression of matrix metalloproteinase (MMP) activity by S1P and specific inhibition of MMP-9 and MMP-13 also protected against glycocalyx loss [36]. These results are consistent with observation in other animal experiments that activated MMPs lead to loss of glycocalyx and increased leukocyte attachment. Further, the actions of agents such as doxycycline that protect the glycocalyx act, at least in part, by inhibiting MMPs [38].

Given the evidence that S1P plays a critical role in protecting the glycocalyx by inhibiting the protease activity-dependent shedding of CS, HS, and the syndecan-1 ectodomain, it is important to understand the regulation of the delivery of S1P to the endothelial surface. Although it is known that activated platelets secrete S1P, the

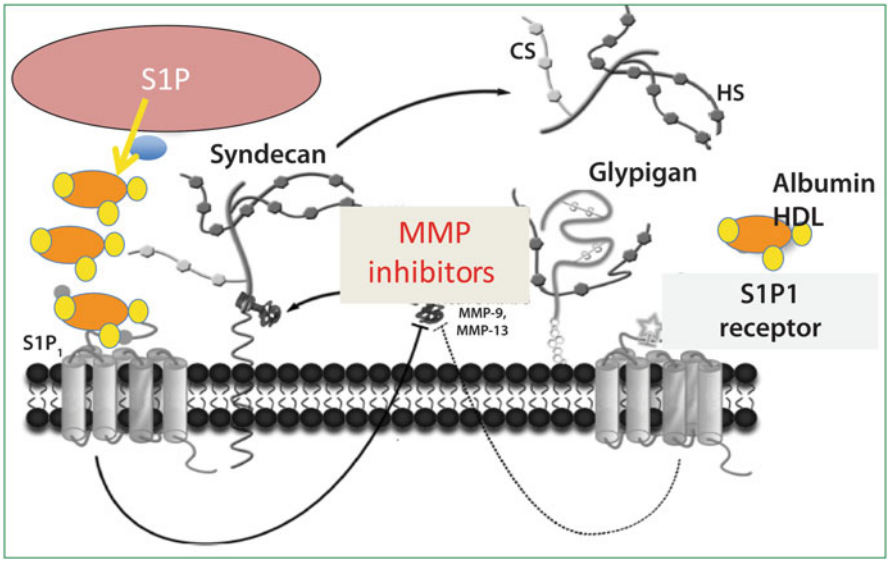


Fig. 3.3 The roles of sphingosine-1-phosphate (S1P) and albumin to stabilize the glycocalyx. Sphingosine-1-phosphate is stored in circulating red cells, released into the circulation bound to albumin and apolipoprotein M in HDLs. Ligation to the S1P1 receptor on endothelium activates signaling pathways 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. See also follow-up report [39] (Adapted with permission from Zeng et al. [36])

primary source of S1P in normal plasma is red cells that synthesize and store high levels of S1P. Albumin not only carries S1P, but also facilitates the release of S1P from unstimulated red cell membranes to the endothelium. The S1P-dependent mechanisms regulating the glycocalyx are illustrated in Fig. 3.3 [36, 39]. It is postulated that various blood conditions may limit S1P delivery to the endothelium. These include reduced synthesis of S1P in diseased or infected red cells, and modified binding/transport of S1P (e.g., albumin or HDL carrier protein glycosylation in diabetes). Also the increased mortality and morbidity described in patients transfused with red cells older than about 14 days may be explained, in part, by reduced S1P synthesis and corresponding loss of glycocalyx protection [40].

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 (ANP) [41], although the mechanism of action is not clear because ANP can also have vasoprotective actions [42–44].

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 earlier, 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 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 electron microscopic 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 the section "Background: Imaging the Glycocalyx: More Detailed Technical Issues," and we have included some Top Tips (Boxes 3.1, 3.2, and 3.3) to help follow the interpretation of the evidence discussed.

Box 3.1

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 ~200 nm for a light microscope, ~40 nm for X-Ray microscope, ~0.003 nm for an electron microscope. However electron optics is very inefficient therefore <1 nm is performing well.

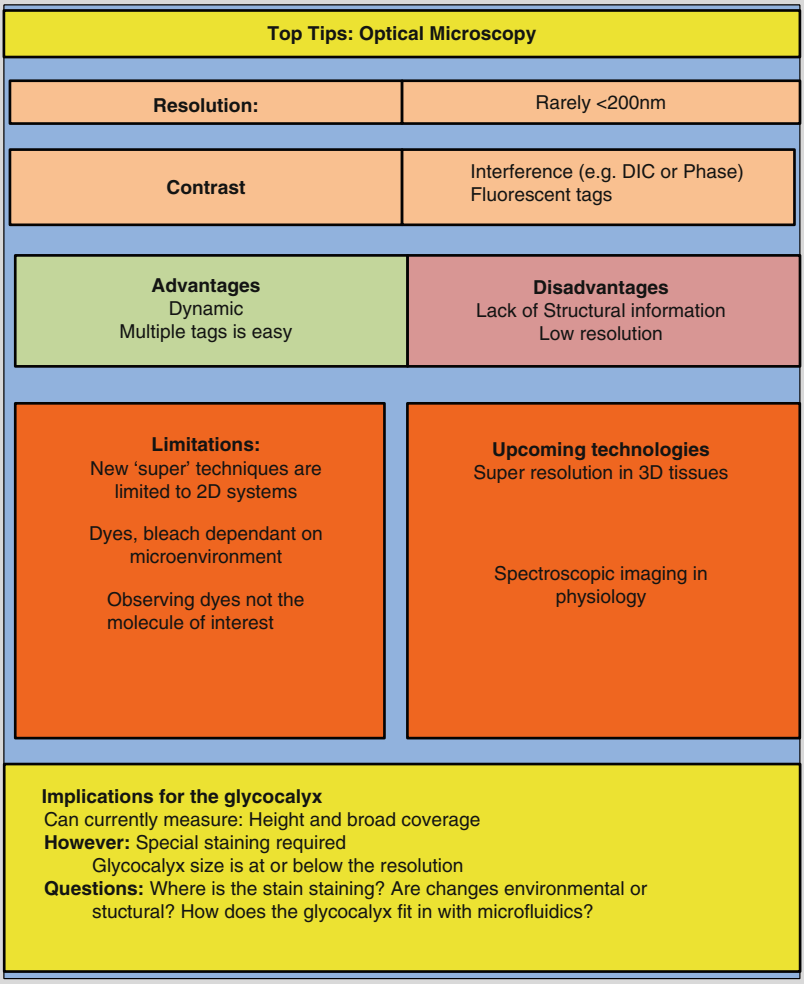
Contrast is not resolution. It is effectively the signal to noise, i.e. how easily one can observe an object, and this depends on the objects interaction with the beam compared to the surroundings. It is possible to observe an object much smaller than the resolution.

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

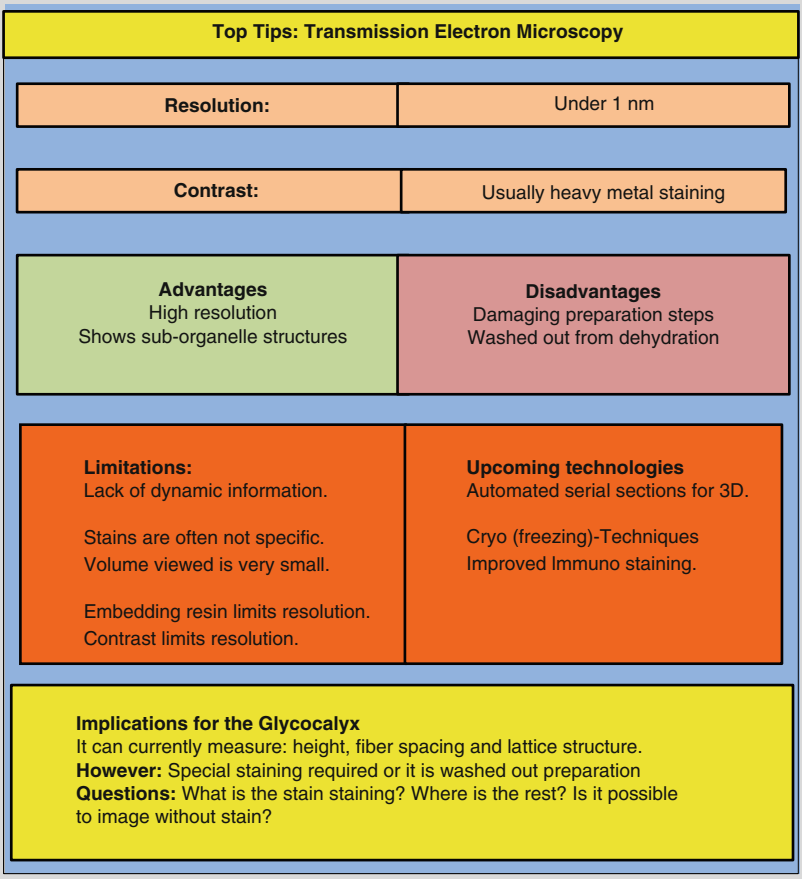
For example: A fluorescent point is where there is an interaction with an object at the time it was imaged.

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.

Box 3.2


Top Tips: Optical Microscopy
Resolution:
Rarely <200nm
Contrast
Interference (e.g. 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 for the glycocalyx
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?

Box 3.3



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 [45, 46], it was suggested that the physical structures that were described in terms of water and solute exchange through "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,

such as 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 [47]. 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 as 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 earlier, 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 microvessels level (some of the extensive background to these studies is reviewed in the first *Handbook of Microcirculation*, published in 1984 [48–51]). 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 [52] 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 inter-endothelial 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 [53]). 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 suggestions 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 [54, 55].

A series of key observations that still form the basis for many current investigations and clinical approaches to investigate the glycocalyx were those by Duling and colleagues in small blood-perfused vessels in situ [56]. As shown in Fig. 3.4, they demonstrated that large dextran molecules (MW greater than 70 KD) were

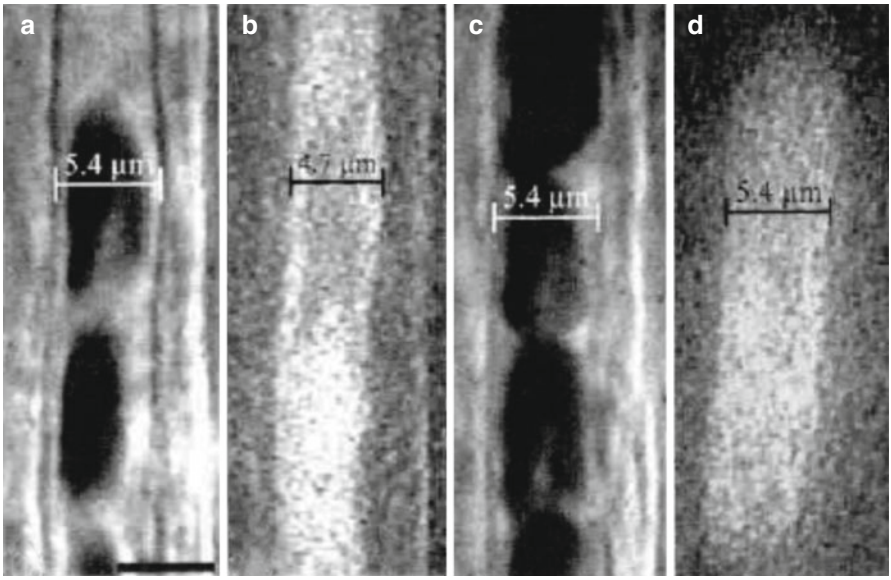


Fig. 3.4 The endothelial glycocalyx excludes large macromolecules such as 70 KD dextran and circulating red cells. Parts **a** and **b** show digitized images of a capillary segment in a normal vessel. The width of both the blood cell column (**a**) and the column of high-molecular-weight FITC-dextran (70 KD) (**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 from Vink and Duling [56])

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 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 KD MW) into the endothelial surface layer [25, 54, 56]. It was soon common to assume that an endothelial surface layer measured using these light microscopy approaches (up to 0.5 µm thick in microvessels) 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 on their size and charge. This ignores the fact that the time constants for

penetration of albumin and dextrans (>40 KD, < 70 KD) 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 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 KD dextrans, 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 [57], these observations indicate that complex diffusion, binding, and chemical interactions compromise simple interpretations of tracer penetration and distribution in the glycocalyx (see later section: "Glycocalyx Volume Measurement in Human Subjects").

In summary, by the end of the 1980s there was a clear understanding that the glycocalyx was a key regulator of microvascular function because it played a major role in regulating plasma and red cell flows through microvessels and in forming 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 Three-Dimensional Layered Structure in Microvessels

As explained in more detail later in the 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 Qvortrup [58], as well as from Arkill et al. [59], demonstrates bush-like structures in the glycocalyx of fenestrated microvessels of rat gut microvessels that project 100 nm from the surface. These structures were preserved using a novel perfluorocarbon perfusion technique. Figure 3.6 summarizes 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 [17]. 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

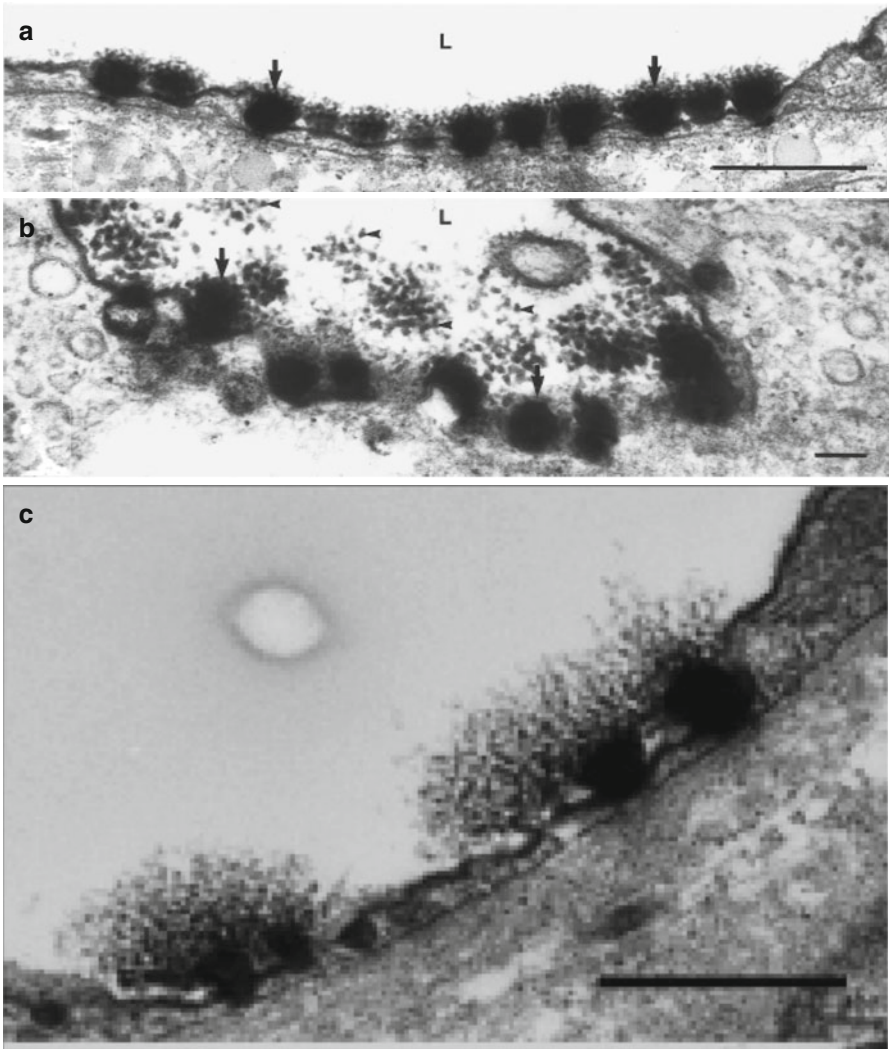


Fig. 3.5 Examples of bush-like structures in the glycocalyx first described in electron micrographs of fenestrated capillaries from the lamina propria of rat small intestine (**a**, **b**) and glomerulus (**c**). The tissue was processed using perfusion fixation with a perfluorocarbon perfusate, glutaraldehyde 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 (Parts **a** and **b** are reproduced with permission from Rostgaard and Qvortrup [58]. Part **c** is reproduced with permission from Arkill et al. [59])

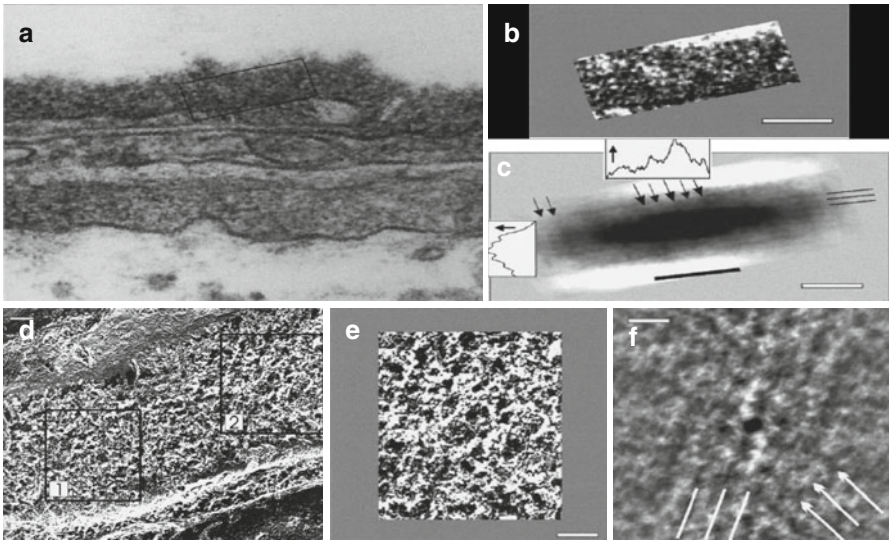


Fig. 3.6 The *top panel* shows regions of a normal capillary from frog mesentery prepared using conventional fixations. Individual microvessels were perfused with Ringers solution containing 40 % bovine serum albumin and ruthenium red prior to fixation with 1 % osmium tetroxide (**a**). The *boxed* region is shown enlarged in (**b**) and the results of autocorrelation 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 suggests 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 Squire et al. [17])

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 structure to the inner glycocalyx. Using the regular bush-like structure observed in the original Rostgaard and Qvortrup study [58] 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 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 sketch of this ultrastructural model is shown in the left panels of Fig. 3.7 [8, 17].

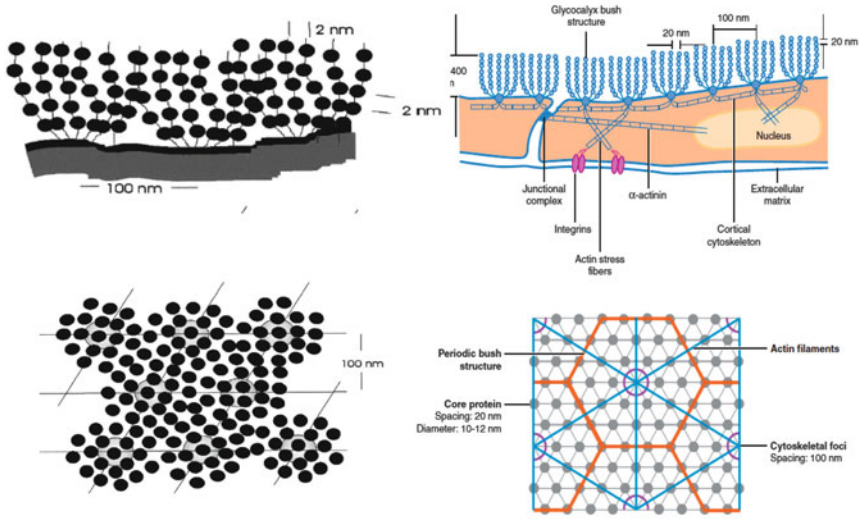


Fig. 3.7 Model molecular configuration of the inner glycocalyx is shown in the sketches on the left showing fibrous strands projecting from the endothelial surface with some periodicity along the strands. Adjacent tufts are separated by 80–100 nm in a hexagonal array. A more formalized schematic is shown 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])

A similar approach performed on archival tissue samples from Rostgaard and Qvortrup's laboratories [59] 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 larger than 80 nm were observed the 100 nm intercluster spacing described above observed was not one of them, perhaps due to amalgamating the fenestrated and nonfenestrated tissues into one result. Interpretation of the longer distances remains inconclusive. To definitely demonstrate it solely by this method, without additional specific labeling, may not be possible. Thus, the sketch in Fig. 3.7 is assumed to be characteristic of the inner regions of the glycocalyx in both nonfenestrated 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]. Nevertheless, the evidence is still quite limited and there are technical limitations to the interpretation of autocorrelation (or Fourier) analyses based on projections through relatively thick specimen. Furthermore, a more useful *en face* view of the glycocalyx cannot be obtained from these approaches, which give mainly a side view of the glycocalyx (see section: "Background: Imaging the Glycocalyx: More Detailed Technical Issues").

As a step toward better 3D imaging of the glycocalyx, a recent study used electron tomographic methods to examine the glycocalyx [60]. 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 earlier, but also allows the image to be rotated to enable *en face* observation of the lateral spacing of the anchoring foci on 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. Thus, as new analyses become available there is a growing consensus that a quasi-periodic structure 200–400 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 the 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 less extensive structures closer to the endothelial surface that have the properties of a molecular sieve. The hypothesis that a layered structure consistent with an 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, 34], and the main conclusions relevant to this chapter are summarized below. With respect to transvascular 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 [61–63]. The result is a steady-state balance between the hydrostatic and colloid osmotic pressures across the glycocalyx to maintain slow filtration as described in the Revised Starling Principle (see Chap. 2). An example of the gradients of albumin concentration at high and low filtration rates is Fig. 3.8 [61].

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 have 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" that reduces the friction between red cells and microvessel wall. For the purpose of this chapter it is instructive to use the results of calculations by Weinbaum et al. and others [64–66] to test whether estimates of resistance to water flow across the glycocalyx (i.e., during transvascular exchange) can also account for the properties of a functional lubricating layer. For example, the Darcy coefficient (K_w, a measure of resistance to water flow) has values in the range of 10^{-13}–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. [66], such a 200 nm thick layer of glycocalyx is sufficient to describe an effective lubrication layer mechanism for red cells (the mechanism is similar to the way a skier crosses powdered snow).

Thus, as often stated in recent reviews, a consistent description of the glycocalyx as both a permeability barrier and an effective lubricating layer is obtained with glycocalyx thicknesses about 200 nm thick with the periodic structure in Fig. 3.7. However, a thicker glycocalyx with the same uniform structure does not provide the same consistent description. The key observation is that while a two- to fivefold increase in thickness of the layer would further improve the micromechanics of red cell fluxes, the same increase in thickness predicts a reduction in transvascular water movement to well below all measured values in microvessels [67]. The problem is resolved if the outer layers of the glycocalyx (thickness L) have less resistance to water flows than the inner layers, as expected if the glycocalyx is better viewed as having an outer structure with porosity with distance from the endothelial surface (as suggested in Fig. 3.9). 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 of more than an order of magnitude less than the inner core. The importance of these conclusions is that methods to investigate the glycocalyx in human subjects such as measurements of glycocalyx volume and visualization of sublingual microvessels can lead to estimates of glycocalyx thicknesses up to several μm in thickness. The assumptions that these approaches provide measures of changes in glycocalyx that are characteristic of changes in the core structure of the glycocalyx (e.g., syndecan-1 release) are not supported by the aforementioned analysis.

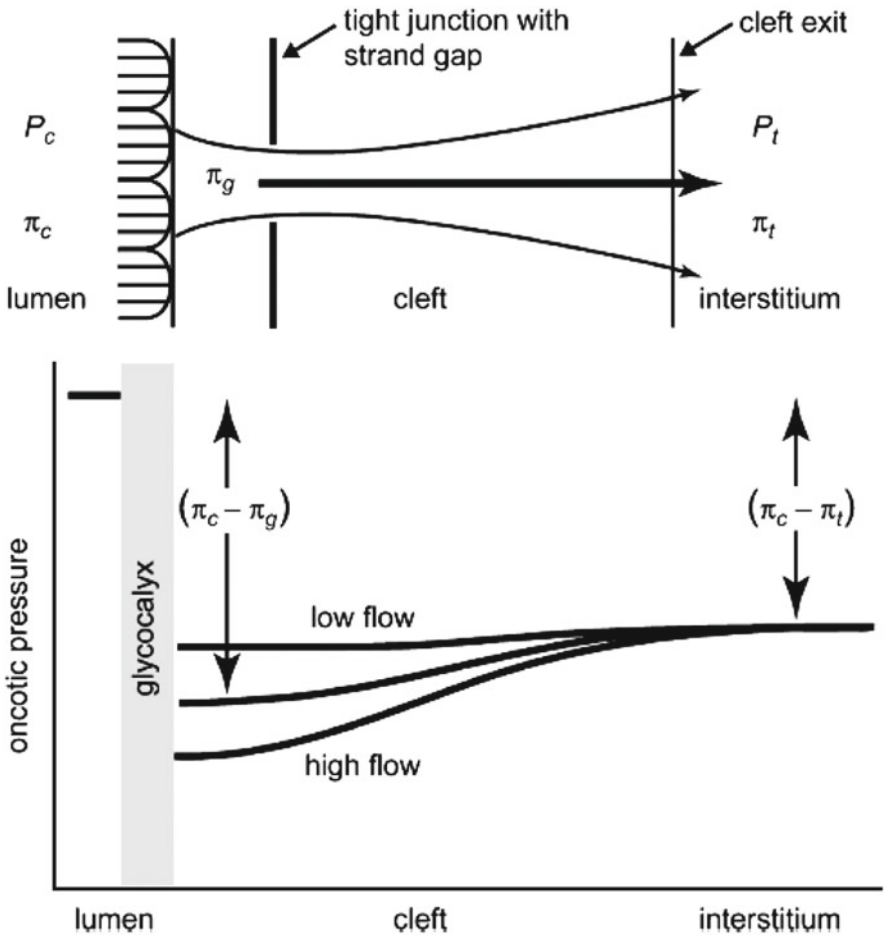


Fig. 3.8 Model demonstrating that the osmotic pressure of the subglycocalyx region is always lower than that in the mixed interstitial fluid in a filtering microvessel. The ultrafiltrate crossing the normal glycocalyx has a low plasma protein content. When funneled into breaks in the junctional strands, 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) (Reproduced with permission from Adamson et al. [61])

Measurement of Red Cell Gap in Human Subjects

To overcome some of the limitations 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 labeled red blood cells (RBCs) and low-molecular-weight dextrans, there has been a renewed focus on noninvasive tools for analyzing

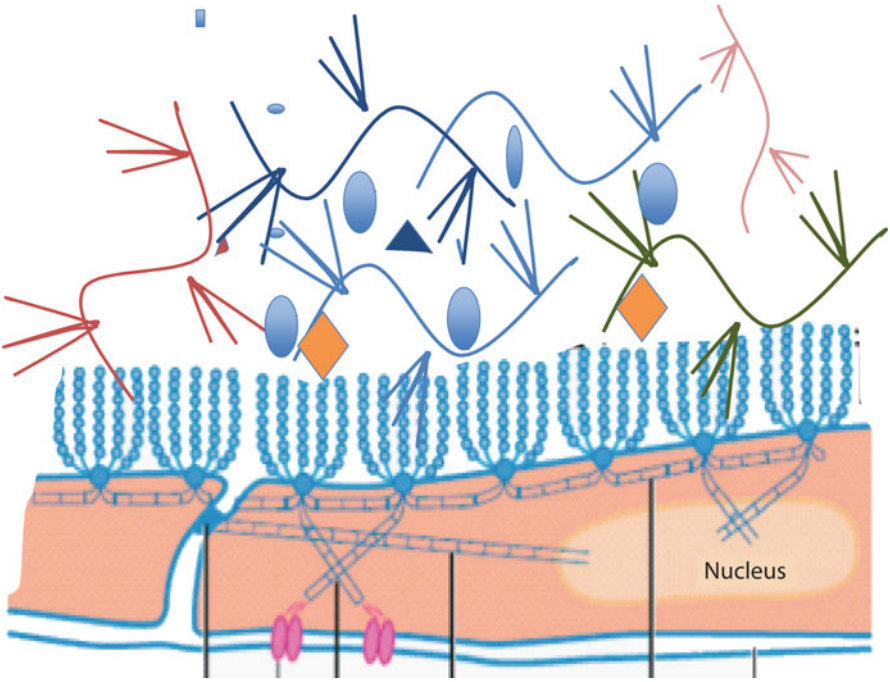


Fig. 3.9 An updated version of the 3D model of the glycocalyx in Fig. 3.7 that combines the quasi-periodic region extending up to 200 nm from the endothelial surface that forms the primary permeability barrier and the more porous outer region with reduced resistance to water and large solute movement. The concentration of tracer macromolecules such as dextrans and albumin within all regions of the glycocalyx is always less than in the plasma (Adapted with permission from Weinbaum et al. [8])

the endothelial surface layers using methods such as sidestream dark field imaging. This technique is based on orthogonal polarization spectral imaging introduced in 1990 to improve the contrast between red cells, the vessel wall, and the background [68]. The 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 [69]. 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) indicated loss of glycocalyx [56]. There has been a rapid succession of reports describing the adaption of the orthogonal polarization spectral approach as sidestream dark field imaging.

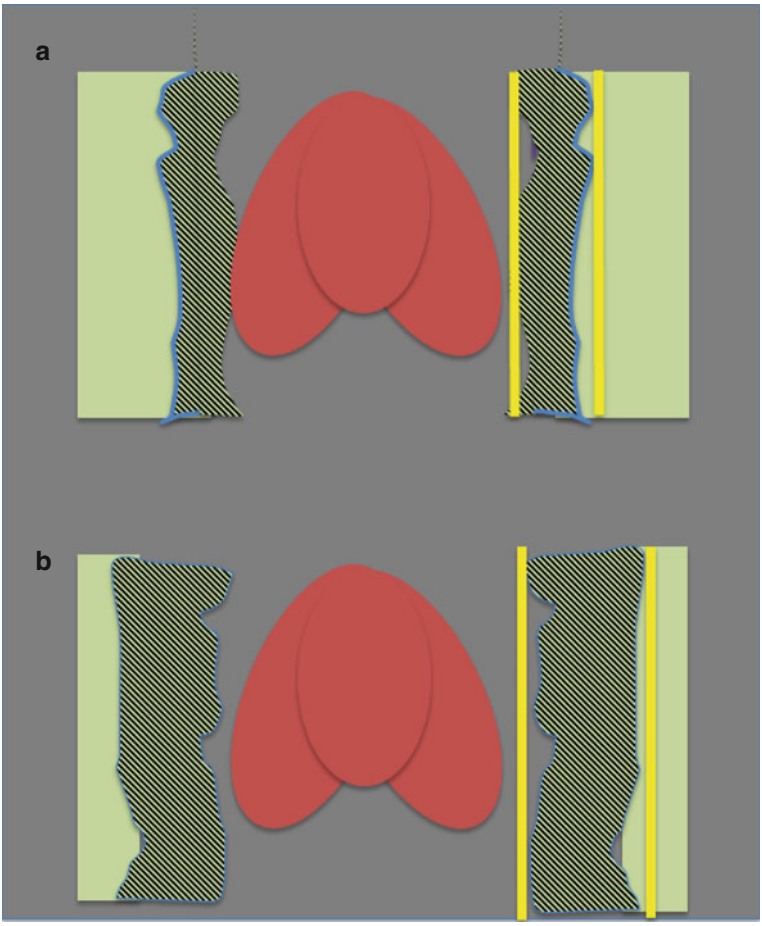


Fig. 3.10 The idea that red cells penetrate closer to the vascular wall when the glycocalyx is damaged in a capillary is being tested as a basis for sidestream dark field imaging in microvessels up to 50 μm diameter in the sublingual vessels of human patients. The dimensions of a perfused boundary region (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 [32])

In some reports technical details are minimal, but the approach appears to have been used in at least three forms [28, 32, 70, 71]. Version 1 measures an ESL thickness in small blood vessels (diameter < 15 μm) as the space between the red cell column and the position of the vessel wall whose position is enhanced by computer image processing. Version 2 (Fig. 3.10) abandons measurements of ESL layer thickness altogether and measures the distribution of the red cell column width at multiple sites (20 or more) along a microvessel segment [32]. A statistical analysis of this distribution of red cell column width 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 [28], 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 [66]. The change in erythrocyte column diameter observed during such widening divided by 2 is related to the dimension of the microvascular glycocalyx.

Over the past 6 years, there have been several (mainly short) reports describing 1 or more of these approaches. In an initial paper, 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 in diameter [28]. 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 later). Furthermore, in the same report, ESL 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 ESL 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 it 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 from 16.4 μm in control subjects to 17.7 μm in dialysis patients [32]. There was no change in the red cell column width (10.5 in control vs 10.1 μm) but the increased perfusion column width indicated a statistically significant increase in PBR to 3.6 ± 0.4 μm compared with 3.3 ± 0.4 μm in healthy controls [32]. 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 syndecan-1 levels reported in the earlier discussion of loss of glycocalyx components were from the same patients). In other preliminary reports, patients with evidence of cardiovascular disease had PBR values of 2.2 ± 0.3 μm compared with 2.0 ± 0.3 μm in controls [71], and in chronically ill patients PBR was 2.7 μm (range 2.6–2.9) compared with 2.46 (2.4–2.7) μm in controls [72]. All reports claim a correlation between increased PBR and

independent criteria for glycocalyx degradation including increased glycocalyx plasma components, inflammatory markers, or measurement of the so-called glycocalyx volume (see later). Because test numbers are low, and details of both the criteria for vessel selection and technical details limited, these conclusions are at best tentative. Furthermore, Amraoui et al. found no correlation of PBR with cardiovascular risk [73]. The relatively small changes in PBR described earlier clearly indicate that the power of the technique to discriminate diseased states from more healthy states may be limited. 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 later), 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 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 microns in diameter [74–77]. Furthermore, independent of changes in the glycocalyx, it is reasonable to propose mechanisms that may change the micromechanics of red cell movement within microvessel 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 changes in the glycocalyx important in relation to perioperative 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 while 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: Revised Starling Principle).

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, which is too often neglected, 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 that 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 [78–80]. Sixty 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 1. While 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) [81], which is 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 liters and a considerably lower value in patients with Type 2 diabetes. As pointed out [82], 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 that are roughly inversely proportionate to their molecular size. This gives rise to a considerable underestimate 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 later). Third, the authors assume the partition coefficient of D40 between the plasma and fluid phase of the glycocalyx to be 1. 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 C_p and C_g 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:

$$\lambda = C_g / C_p \tag{3.2}$$

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

$$m = C_p V_p + C_g V_g = C_p V_p + \lambda C_p V_g = C_p \left(V_p + \lambda V_g \right) \tag{3.3}$$

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 $\lambda = 1$; that is:

$$m / C_p = V_p + \lambda V_g \tag{3.4}$$

Since λ is unknown, only λV_g can be estimated by subtracting V_p from m/C_p. Furthermore, changes in the value of m/C_p are open to misinterpretation. If the thickness of the glycocalyx is reduced without change of λ, apparent glycocalyx volume, λV_g, 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, λV_g. 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 [83, 84]. This method arose from measurements of red cell and plasma volume of patients subjected to preoperative volume loading with colloid solutions, which were either 5% albumin or 6%

hetastarch solutions [84]. It is argued that plasma volume estimated from the distribution volume of indocyanine green (ICG) can be divided into a circulating component and a noncirculating component. The noncirculating 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 noncirculating component of the plasma is calculated by subtracting the circulating component from the volume of distribution of the ICG. Rehm and colleagues [84] estimated mean values for the noncirculating component in the range of 700 ml in patients before volume loading and 300 ml afterward.

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 [85] indicate that rates of penetration of labeled albumin and fibrinogen 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 more than 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 [86]. 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 noncovalently 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 noncirculating component. It was appreciated by the 1950s 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 Chap. 2: Revised Starling Principle). The flow of cells, F_c, or plasma, F_p, 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 V_p divided by its mean transit time, t_p. Measurements of the mean transit times of labeled 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 t_c/t_p through the pulmonary circulation are in the range of 0.98–0.99, the ratio for the liver is closer

to 0.5 [87]. If plasma volume is estimated from red cell volume and large vessel hematocrit, then since:

$$H_{LV}/100 = F_c/\left(F_c + F_p\right) = 1/\left(1 + F_p/F_c\right) = 1/\left[1 + \left(V_p/V_c\right)\cdot\left(t_c/t_p\right)\right]$$

and

$$V_p = V_c\left(t_p/t_c\right)\left[\left(1/H_{LV}\right) - 1\right] \tag{3.5}$$

If the whole body hematocrit were substituted for H_{LV}, the term t_p/t_c would not be part of the expression. Rehm et al. and Jacobs et al. minimize the errors introduced by assuming $t_p/t_c = 1$ by using the hematocrit of arterial blood [83, 84]. 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 t_c/t_p through the pulmonary circulation remains close to 1, considerable error may be avoided. If hematocrit is determined from the venous blood, however, fluctuations in t_c/t_p 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 noncirculating 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:

$$m/C_p = V_p + \lambda V_g + m_b/C_p \tag{3.6}$$

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 C_p falls as circulating tracer is removed by the liver. This could be mistaken for an increase in the noncirculating component of plasma volume. Alternatively, if repeated estimates of plasma volume are made, the failure of the 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.

It is also noted that in a detailed review of the ways new understanding of the fluid exchange through the glycocalyx helps clinician to evaluate fluid therapy (for details see Chap. 2: Revised Starling Principle), 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. 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 is 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 liters imply a glycocalyx thickness, averaged over the surface area of the human vasculature of 2–3 μm (assuming surface area of 350 m^2 [77]). Part of the confidence in the sidestream 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 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 [88]. In addition to lending support to the hypothesis that thinning of the glycocalyx might be a precondition for the development of atherosclerosis, these and related measurements using two photon microscopy [89] and fluorescein isothiocyanate (FITC) dextran exclusion [90] have led to broad acceptance that glycocalyx regions of several microns may be common in larger vessels. As a step toward 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. 3.3 and the method used to make such measurements may bias values. To apply sophisticated imaging in the larger vessels described previously (150 microns 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 earlier section about S1P and glycocalyx stability: *Restoration and Preservation of the Glycocalyx*) that in mammalian vessels such low albumin concentrations do not maintain S1P concentrations in the range where it can stabilize the endothelial barrier and suppress MMP release. Thus, as described earlier (and see [36]), 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 Versus 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. Superresolution light microscopy can, in ideal circumstances, have resolutions circa 30 nm, but as above, this ideal limit is not reached in samples containing the glycocalyx. 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. In the following paragraphs, we review additional limitations imposed by the requirement to prepare wet biological samples to be processed for sample analysis in a vacuum and to improve contrast by additional staining of selected glycocalyx components [91, 92].

Tissue Preparation

Since the late 1940s, 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; ultrathin 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 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 makes the glycocalyx difficult to study. Another is that it resides at an interface where differences exist 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 mucopolysaccharides can be far from straightforward. 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 product 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 similar to cupromeronic blue, binds relatively selectively to proteoglycans. The advantage of such copper-based stains is that they can also be seen easily with optical histology, helping in the selection of areas of interest to section for electron microscopy [91, 92]. Another common stain is lanthanum, containing dense highly positively charged ions favored by the Chappel group [93, 94]. 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) [60, 95]. 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. The longer spacings observed between periodic densities are broadly in agreement with previous data [96]. 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 reexamine 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. In a preliminary report, 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 [97].

Biological electron microscopy has broadened, particularly in the last decade, to routinely fill more scale range, and lose less biological content in the processing. Cryo-electron microscopy makes use of a noncrystalline 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. 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 earlier in the section: "The Glycocalyx as a Three-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 [98]) have as yet been less satisfactory.

Until recently, reconstruction of 3D images of endothelial structures on scales greater than 1 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 the LaDy GAGa 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.

Conclusion: Frequently Asked Questions

The follow 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 affect perioperative 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 perioperative 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 cell 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 major determinant of the effectiveness of perioperative 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 Chap. 2 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 a dimension 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 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 stabilize 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 (key issues item 1 listed above), it is not clear that addition of albumin to infusion fluids would improve the stability of the glycocalyx because albumin concentrations required for glycocalyx stabilization and S1P delivery are low.

The first aspect of item 2 of the key issues list is to consider 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 overhydration 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 the 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 (item 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 (e.g., dextran). If the subtle interaction of HES transport by diffusion and coupled water flows leads to HES accumulation in the subglycocalyx 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 heparan sulfate or hyaluronan), causing loss of plasma fluid to the extravascular space because of the transvascular leak of plasma macromolecules.

With respect to questions about the restoration of the glycocalyx under conditions where key components are lost (item 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 perioperative period (item 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 that 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 in the inflammatory cascade may be just as important as the mechanical forces in determining leukocyte interactions when the glycocalyx is damaged. 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 (item 5), it is noted that although electrostatic charge effects influence the organization of the glycocalyx matrix fibers, and that both red cell aggregation and adhesion of red cells to endothelium under static conditions can be modified by electrostatic interactions, the dynamics of red cell flows through microvessels at normal microvascular flow rates 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 [99].

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Chapter 4
Techniques for Goal-Directed Fluid Management

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 (mini-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 mini-fluid bolus (500 ml crystaloid) approach mini-bolus (500 cc crystaloid) to fluid therapy is recommended.

Keywords Fluid responsiveness • Fluid therapy • Resuscitation • Hemodynamics • Hypovolemia • Operating room • Glycocalyx • Intensive care units (ICU) • Critical care • Perioperative • Goal-directed fluid management • Passive leg raising maneuver • Fluid bolus • Mini-fluid bolus

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.

P.E. Marik, MBBCH, FCP(SA), FCCM, FCCP
Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Eastern Virginia Medical School, Norfolk, VA, USA
e-mail: MarikPE@evms.edu

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3. Only about 50 % of hemodynamically unstable patients are volume responders.
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 recent 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

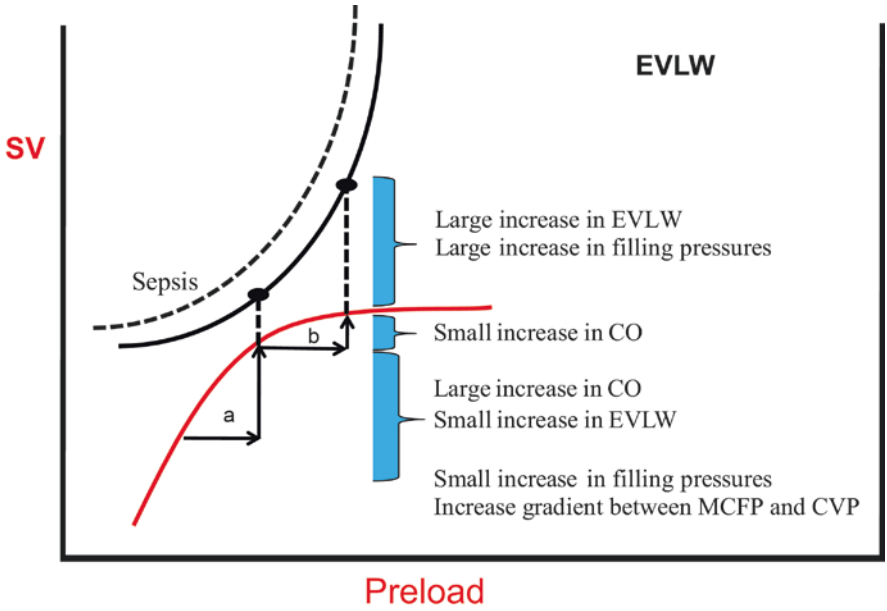

Fig. 4.1 Superimposition of the Frank-Starling and Marik-Phillips curves demonstrating the effects of increasing preload on stroke volume and lung water in a patient who is preload responsive (**a**) and nonresponsive (**b**). With sepsis the EVLW curve is shifted to the left. *EVLW* extravascular lung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

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 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 updated Surviving Sepsis Campaign Guidelines (April 2015) recommend "Repeat focused exam by a licensed independent practitioner including vital signs, 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

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

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 (April 2015 update) [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. recently 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].

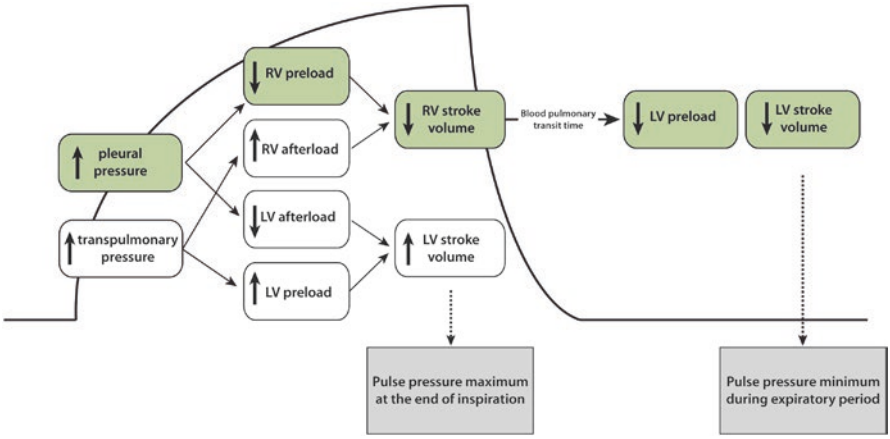

Fig. 4.2 Heart-lung interactions during mechanical ventilation to assess volume status. The cyclic changes in left ventricular (*LV*) stroke volume are mainly related to the expiratory decrease in LV preload due to the inspiratory decrease in right ventricular (*RV*) filling

"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, 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

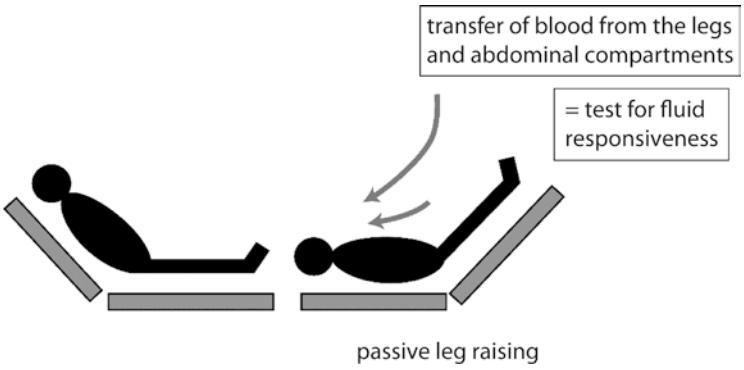

Fig. 4.3 Passive leg raising (PLR) maneuver

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

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 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 (mini-bolus) 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 Mini-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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Chapter 5
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.

Keywords Echocardiography • Fluid responsiveness • IVC collapsibility index • SVC collapsibility index • Delta velocity time integral percentage • Passive leg raising • Fluid management • Doppler ultrasound • Goal directed fluid therapy • Stroke volume • Cardiac output

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.

M. Argalious, MD, MSc, MBA, MEd
Cleveland Clinic Lerner College of Medicine, Center for Anesthesiology Education, Anesthesiology Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: argalim@ccf.org

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3. Echocardiographic "dynamic" measures of fluid responsiveness including IVC and SVC collapsibility index and respiratory variations in left and right ventricle 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.

Table 5.1 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

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.

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 5.1) [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. 5.1). 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. 5.2) 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.

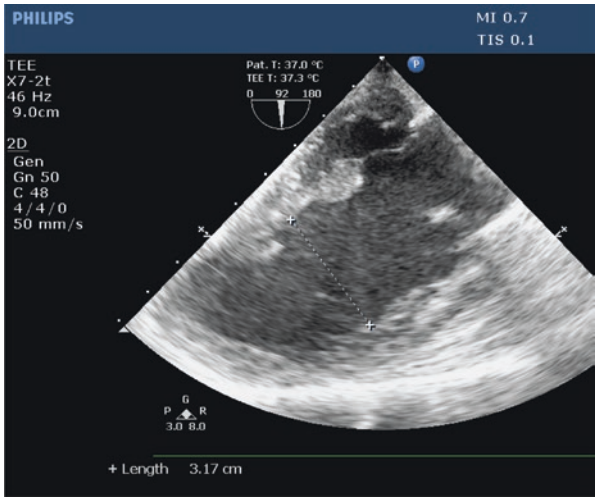

Fig. 5.1 Transesophageal echocardiographic measurements of left ventricular (LV) minor-axis diameter (LVD) from transgastric 2-chamber view of LV, usually best imaged at an angle of approximately 90–110°

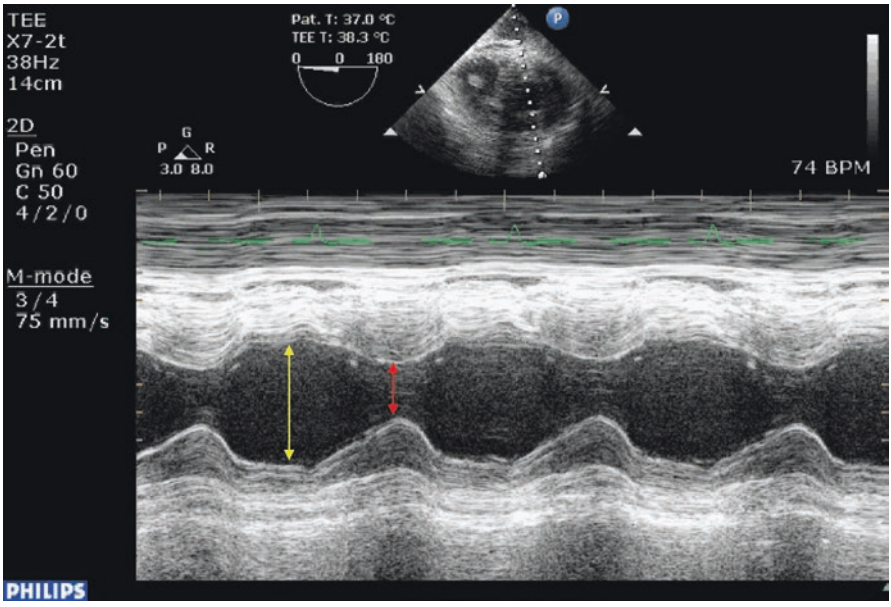

Fig. 5.2 Transesophageal M-mode imaging through the transgastric mid short axis view identifying end-diastolic (*yellow arrow*) and endsystolic (*red arrow*) left ventricle internal diameters

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 importance of measuring both end-diastolic and end-systolic left ventricle dimensions to differentiate hypovolemia from other conditions (Table 5.1).

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].

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 5.2 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].

Table 5.2 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

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:

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

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. 5.3).

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

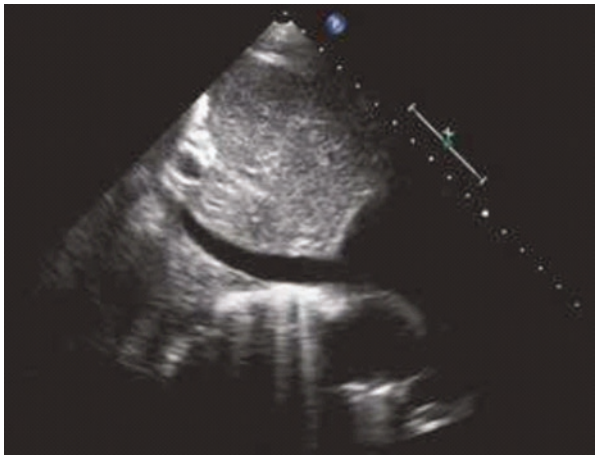

Fig. 5.3 Transthoracic subcostal view of the IVC

should be measured 2–3 cm before it merges with the right atrium. IVC collapsibility index is measured as follows:

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

Uses of IVC collapsibility index in spontaneously breathing patients:

1. IVC diameter and collapsibility can be used to estimate right atrial pressures (Table 5.3) [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

Table 5.3 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

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:

$$\text{SVC collapsibility index} = \text{Maximum Diameter SVC}\left(\text{DSVC max}\right) - \text{Minimum Diameter SVC}\left(\text{DSVC min}\right) / \text{Maximum Diameter SVC}\left(\text{DSVC max}\right) \times 100 \left(\text{Fig. 5.4}\right)$$

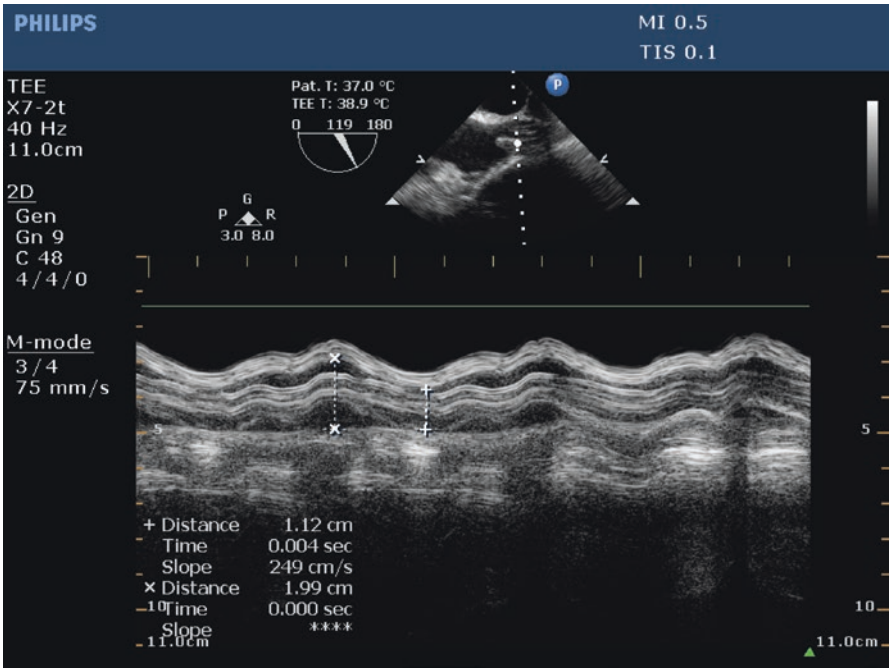

Fig. 5.4 M-mode Assessment of SVC collapsibility index utilizing the TEE midesophageal bicaval view at ~120°. SVC collapsibility index = 1.99 cm − 1.12 cm/1.99 cm × 100 = 43 % indicating fluid responsiveness. Note the echogenic density in the SVC representing an indwelling central venous catheter that should not be confused with the wall of the SVC

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. 5.4):

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.
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:

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

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:

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

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

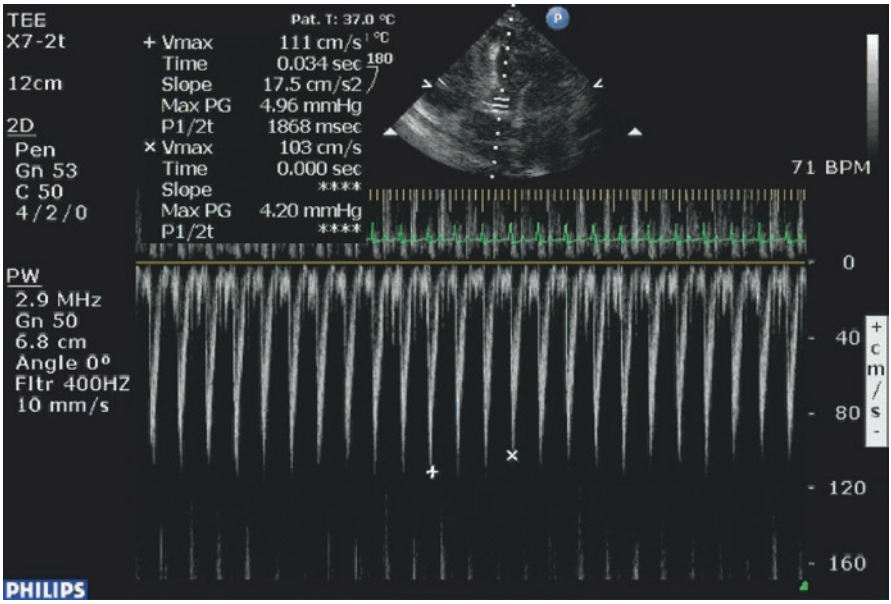

Fig. 5.5 TEE Assessment of Delta V peak in the deep transgastric 5 chamber view. Delta V peak = $111_{cm/s} - 103_{cm/s}/(111_{cm/s} + 103_{cm/s}/2) \times 100 = 7.5\,\%$ indicating lack of fluid responsiveness

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. 5.5).

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. 5.6). This is especially important when transgastric views cannot be obtained for assessment of left ventricle stroke volume changes.

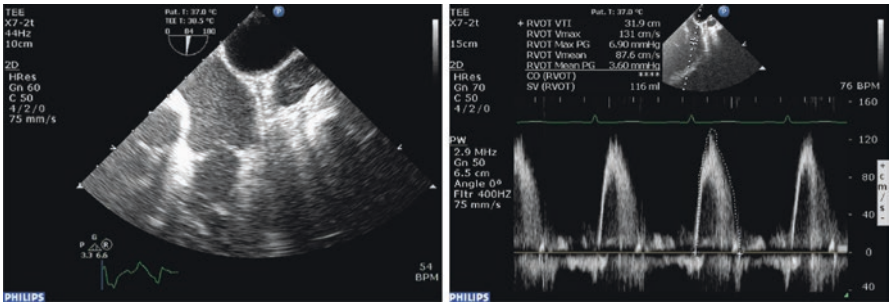

Fig. 5.6 TEE assessment of delta VTI % or delta Vpeak % can also be done using the upper esophageal aortic short axis view so that the pulsed wave Doppler signal is parallel to the right ventricle outflow tract

Esophageal Doppler devices introduced through the mouth and adjusted to obtain the highest Doppler velocity signal from the descending aorta have also been used successfully to assess fluid responsiveness by measuring variations in aortic blood flow (ABF) using the following formula:

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

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:

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

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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Chapter 6
Microcirculatory Blood Flow as a New Tool for Perioperative Fluid Management

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 have been related to the outcome of these patients. This systematic review will report to which extent 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 a significant variability among the patients. Timing of the intervention has a huge impact, as early interventions often lead 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 from its systemic effects and can thus not be predicted by changes in cardiac output or blood pressure. Changes in lactate or in venoarterial PCO_2 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.

Keywords Microcirculation • Tissue perfusion • Cardiac output • Fluids • Lactate • PCO_2

D. De Backer, MD, PhD
Department of Intensive Care, CHIREC Hospitals, Université Libre de Bruxelles, Braine L'Alleud, Brussels, Belgium
e-mail: ddebacke@ulb.ac.be

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Key Points

1. Microvascular alterations frequently occur in the perioperative setting.
2. Fluids improve functional capillary density, but this effect can be variable.
3. The microvascular effects of fluids cannot be predicted from their systemic effects.
4. An improvement in microvascular perfusion after fluid administrations is associated with an improvement in organ function.
5. The impact of red blood cell transfusions is highly variable.

Introduction

Tissue perfusion is often altered in the perioperative setting, as a result of decreased organ perfusion associated with 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. The author performed a systemic review (PubMed search, January 2016, using the following key words: 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 6.1). These are due to several factors including bleeding, impaired cardiac function, infection, tissue trauma, and 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 with some predisposing factors related to the host such as advanced age, chronic cardiovascular diseases, diabetes, cirrhosis, etc. These factors will also affect the microvascular response to fluids.

Table 6.1 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

Hypovolemia (bleeding) and impaired cardiac function (either preexisting or induced by anesthetic agents or sepsis) may result in an impaired cardiac output that 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 alteration 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 with regard to oxygen requirements of the perfused area. These kinds of alterations generate pouches of hypoxia in close vicinity to an 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 nonperfused 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 to 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 noncardiac surgery, we demonstrated that microvascular alterations occur already at the onset of anesthesia,

worsen during the surgical procedure, and slowly recover afterward. [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 to organ dysfunction [11].

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 carries the risk of inducing hemodilution. The impacts 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 increase in viscosity is associated with a decreased resistance to flow and hence improves perfusion, especially at the capillary level [12]. At low hematocrit, the decrease in viscosity may favor vessels collapse and thus impair flow [13].

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 fluid administration may impair tissue perfusion by increasing venous pressure. Even though it was reported in one observational trial that a high central venous pressure (CVP) 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) [14].

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 [15].

In experimental studies, fluid administration resulted in an improvement of microvascular perfusion [16, 17]. In patients submitted to high-risk surgery, administration of fluids improved microvascular reactivity [18]. In patients with septic shock, fluid administration was usually associated with an improvement in the proportion of perfused capillaries resulting in an increased perfused vascular density [19–23], even though some individual variability in the response was observed. When microvascular perfusion increased, it also decreased heterogeneity between areas [19], further indicating that the diffusive component of the microcirculation markedly improved. It also resulted in a decrease in venoarterial and earlobe tissue PCO_2 gradients [24], which are indirect markers of microvascular perfusion [25, 26].

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 [22, 27]. Importantly, the microvascular response in these various studies was dissociated for the systemic response [19–21]. The improvement in microvascular perfusion was observed in patients responding or not to fluid challenge by an increase in cardiac output or arterial pressure [19]. On the other hand, patients increasing their cardiac output or blood pressure in response to fluid did not always experience 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. 6.1 [19]), highlighting that microvascular perfusion is

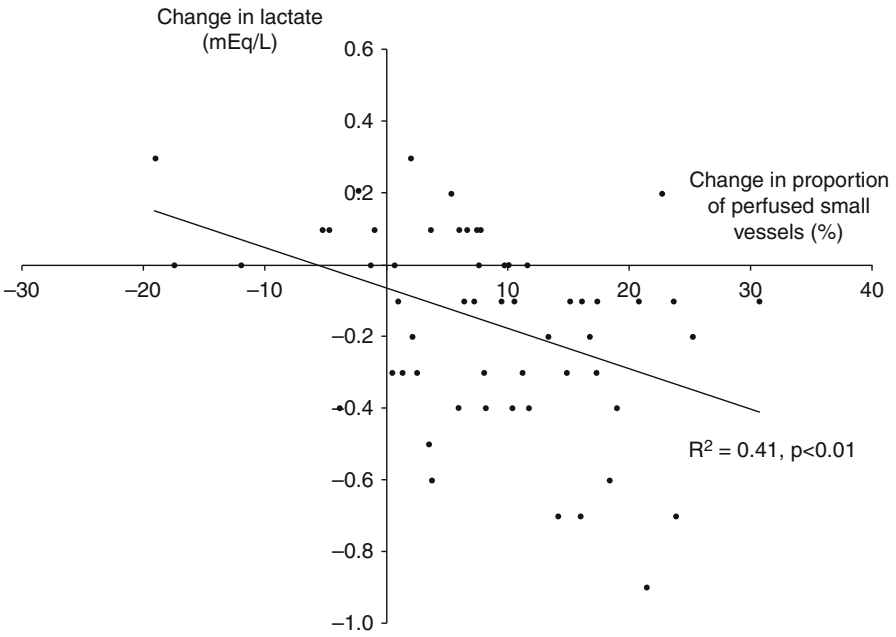

Fig. 6.1 Relationship between changes in microvascular perfusion and changes in lactate levels (Derived from Ospina et al. [19])

the key determinant of tissue perfusion. At the bedside, changes in lactate and veno-arterial PCO_2 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 [22].

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 [28]. In patients with septic shock, fluids improved microvascular perfusion when administered within 24 h of the onset of sepsis but not after 48 h [19].

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 [29–32].

In experimental studies, colloids often increase more significantly microvascular perfusion compared to crystalloids both in ischemia reperfusion injury [32] and in sepsis [16]. In addition, colloids also had a favorable impact on adhesion of white blood cells and platelets to the endothelium [16, 32]. 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 [19]. These results contrast with the findings of Dubin et al. [33], who reported that hydroxyethyl starch better preserved the sublingual microcirculation of patients with septic shock compared to crystalloids. Of note, the microcirculation was not evaluated at baseline, making it difficult to differentiate a positive impact of the type of fluid from an imbalance at baseline in this very small series of patients. 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 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

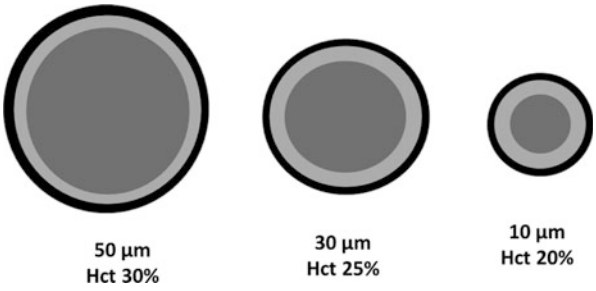

Fig. 6.2 Microvascular hematocrit differs according to the size of the vessel. Due to a mandatory plasma layer of a few microns at the surface of the endothelium, the microvascular hematocrit decreases with vessel size

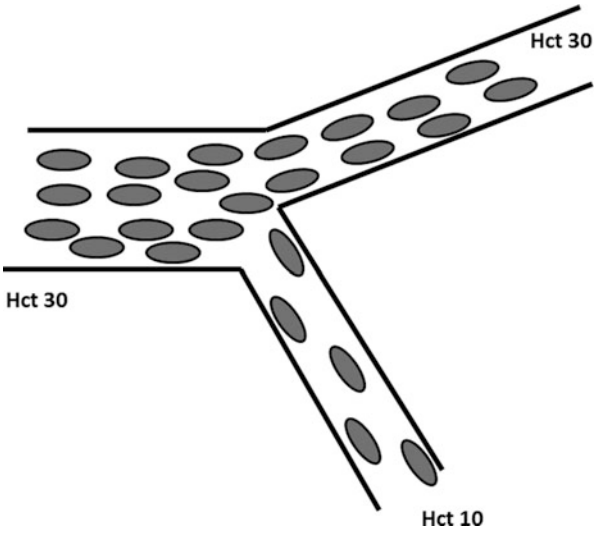

Fig. 6.3 Variability of hematocrit in branch vessels. Due to kinetic inertia of red blood cells, hematocrit is higher in vessels with minimal angle with source vessels compared to vessels with larger angle

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. 6.2). In addition, the distribution of hematocrit varies at bifurcations due to kinetic inertia of red blood cells: Hematocrit is larger in vessels with small angles according to the originating vessel than in vessels with larger angles [34] (Fig. 6.3).

While experimental studies often demonstrated an improvement in microvascular perfusion and tissue oxygenation with red blood cell transfusions [35, 36], their effects are more variable in perioperative or septic patients [37–41]. In patients submitted to cardiac surgery, transfusions increased capillary density but not microvascular flow [40]. In another series of postoperative patients, the effects of transfusions were more mitigated [41]. In patients with sepsis, there were no effects in most trials [37, 39, 42], while some others found beneficial effects [38].

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 effects in some patients, absence of effects in others, and markedly negative effects in the remaining patients. The magnitude of the effect is far above the intrinsic variability of the measurements. The direction of the effect may 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 [37, 39]. The effects of transfusions on the microcirculation were not related to baseline hemoglobin levels nor with the changes in systemic hemoglobin levels [37, 39].

Based on preclinical observations [36], it has been suggested that transfusions of young red blood cells but not old red blood cells could improve the microcirculation. In a limited-size, single-center 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 [41]. In other trials, the age of red blood cells did not affect the response to transfusions in critically ill patients [42] and in septic patients [37]. 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 [43].

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 [19, 44], 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 semiquantitative scores [45], which can even be reliably performed by trained nurses [46].

Indirect measurements can be used. Tissue PCO_2 and venoarterial PCO_2 gradients are particularly attractive. Tissue PCO_2 reflects the balance between CO_2 production (and thus metabolism) and perfusion, and therefore can be used to indirectly evaluate tissue perfusion [25]. Tissue PCO_2 can be measured by contact probes at

earlobe or on the stomach (but gastric tonometry is no more available) [24]. Tissue PCO_2 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 PCO_2 ($PvaCO_2$) can also be used to evaluate microvascular perfusion. In a series of 75 patients with septic shock in whom sublingual microcirculation and $PvaCO_2$ were measured, a $PvaCO_2$ greater than 6 mmHg is associated with moderate alterations in sublingual microcirculation and values above 10 mmHg were associated with very severe microvascular alterations. More importantly, changes in $PvaCO_2$ were inversely related with changes in microvascular perfusion [26].

Conclusion

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 from 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.

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Chapter 7
Mean Systemic Filling Pressure Is an Old Concept but a New Tool for Fluid Management

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 noninvasive or minimally invasive methods. However, the significance of this new 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 baroreceptors via α(alpha)-adrenergic stimulation and to chemoreceptors. The vasoconstriction affects significantly the capacitance of the system by shifting blood between the stress and nonstress volume compartments. The mean systemic filling pressure (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 hemodynamic variables can provide valuable information to correctly understand the cardiovascular status of critically ill patients and better managing fluid therapy and cardiovascular support. Future studies using Pmsf will show its usefulness for fluid administration.

H.D. Aya, MD (✉)
Adult Critical Care Directorate, St George's University Hospitals,
NHS Foundation Trust and St George's University of London, London, UK
e-mail: hollmann.aya@nhs.net

M. Cecconi, MD, FRCA, FICM, MD(UK)
Anaesthesia and Adult Critical Care Directorate, St George's University Hospitals,
NHS Foundation Trust and St George's University of London, London, UK

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Keywords Mean systemic filling pressure • Pmsf • Venous system • Arterial baroreceptor reflex • Chemoreceptor reflex • Capacitance vessels • Venous tone

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 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 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 (MCFP) is that parameter that can quantify the intravascular filling independently from the cardiac function: it is the 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. 7.1). 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.

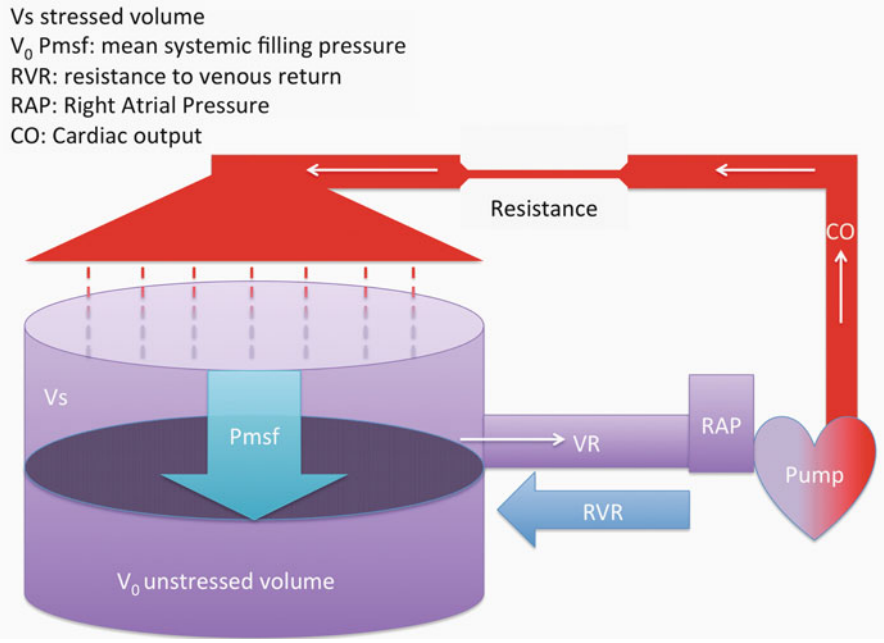

Fig. 7.1 Model of the systemic circulation. Circulatory model with two reservoirs: the big venous reservoir, mainly located in the splanchnic venous territory and the small reservoir, just before the pump: the right atrium. The bigger size of the venous segments suggests a bigger volume and also a greater 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 (VE) will imply necessarily a pressure rise and an elastic distension of the wall of the tube, which depends on 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 stretch of the 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 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 (CO) and central venous pressure were maintained at a constant level. The isolated carotid sinus pressure (ISP) was lowered or raised in 25 mmHg steps between 75 and 200 mmHg. 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 mmHg, whereas when the arterial blood pressure was controlled at 75 mmHg, 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-mmHg 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 sinuses 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 mmHg 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 mmHg 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 reflex venoconstriction 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 that in a preparation where dogs were pump perfused from a blood reservoir and oxygenator to which venous blood returned, during hypoxia (SaO_2 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 nonreflex effect on CO and Pmsf [22]. Severe hypercapnea ($PaCO_2$ to 114 mmHg [15.2 KPa]) caused an increase in Pmsf by 5.5 mmHg, whereas a PaO_2 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 arter-

ies [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 (RVR) 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. Hainsworth et al. [54] studied the response of splanchnic vascular capacitance to changes in carotid sinus pressure in anesthetized 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 mmHg (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 mmHg. 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 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 MCFP.

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 flow of blood 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 mmHg within a few seconds after the hearts of normal dogs were fibrillated and before vasomotor reflexes could develop
- 17.0 mmHg 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] introduced 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 mmHg, while in a dog under total spinal anesthesia the MCFP fell to 5 mmHg. 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 mmHg. At very high rates of epinephrine infusion the MCFP was still rising 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 independent of flow, except the PMSF. However, from a physiological perspective it does not make any sense that the heart (the pump) controls the blood flow. Quite the opposite, the normal heart finely matches the metabolic demand with the oxygen delivery. That is why in this maybe over-simplified model, the Pmsf, which is complexly regulated by the sympathetic system, governs the 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 mmHg.

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 mmHg. This only increased to 22 mmHg after PLR and to 26.9 mmHg 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 mmHg after PLR and by 5.8 mmHg 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 inspiratory-hold maneuver with the values of Pmsf. An increase in the intrathoracic pressure increases the RAP and the pressure backward in the venous territory. 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. Then, probably, this method overestimated the real value of the Pmsf.

Parkin and Wright [73] 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 [74]. 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 10 patients in acute renal failure receiving continuous vein-venous hemofiltration [75]. 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 [76]: Pmsa increased similarly in responders and nonresponders, as expected but interestingly CVP increased more in nonresponders, neutralizing the changes in the gradient of pressure of venous return as described by Guyton.

Recently, Gupta et al. [77] 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 [78] 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 [79]. 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. [80] compared these three 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 nonsignificant 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 [81] 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 mmHg. 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 seems crucial as the effect of an intact sympathetic system is essential to determine the real value of the Pmsf, as discussed earlier [9, 82, 83]. 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 [76, 80, 84].

Should the Venous Tone Be Monitored at Bedside? Practical Implications

Unfortunately, despite the importance of venous tone on the maintenance of cardiovascular stability, there is still very 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 average standardized distance [ASD] from the center of the target 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.

However, 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,

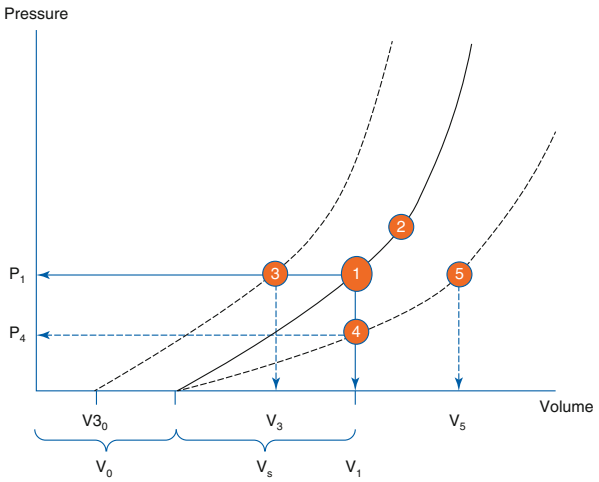

Fig. 7.2 Volume-pressure relationship in the venous compartment. The point 1 represents the total blood volume at the mean systemic filling pressure P_1. For this point, the volume at 0 pressure is the unstressed volume (V_0) and the difference between the total volume (V_1) and V_0 is the stress volume (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 (V_3) 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 (P_4). To return to P_1, volume must be expanded (V_5) unless compliance is corrected

especially in the presence of elevated intravascular filling pressures [87]. The similar principle applies to the Pmsf. A fluid challenge should be used to assess fluid responsiveness particularly in the presence of high Pmsf values. In addition, a fluid challenge can be used not only to test fluid responsiveness but also, as spotted by Maas and colleagues [88], to assess systemic compliance. Given that Pmsf is the pressure at the pivot point, which is located at the venules territory, 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/mmHg. 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 [89] 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. 7.2). 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 circulation and affects, along with the cardiac function, venous return. As this pressure is theoretically located in the postcapillary territory, the reflexes that affect the venous reservoir affect the Pmsf. Three methods have been described to measure Pmsf at bedside in patients with intact circulation. This variable can be now integrated to evaluate the intravascular filling and to explain the pathophysiology of the states of shock at the bedside.

Conflict of Interest Hollmann D. Aya received financial support for educational programs and for attending symposia from Applied Physiology and LiDCO.

Maurizio Cecconi received honoraria for speaking at symposia, financial support for educational programs, and honoraria for advisory board from Edwards Lifesciences, LiDCO, Deltex, Applied Physiology, Massimo, Bmeye, Cheetah, and Imacor.

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Chapter 8
Restricted or Liberal Fluid Therapy

Thomas E. Woodcock

Abstract While extreme fluid deprivation and fluid overdose resulting from negligence or misinformed prescription are undoubtedly harmful, observations and experiments do not point to fluid therapy as a significant determinant of patient outcomes from major surgery. Therapy maintaining fluid balance less than 2 l is probably optimal. There are two interdependent fluid circulations (blood and interstitial fluid) serving the needs of cells and intracellular fluid. Filtration rate (J_v) of fluid from the blood circulation to the interstitial circulation is a major determinant of the dynamic equilibrium between plasma volume and interstitial volume. It is affected by anesthesia and by vasoactive agents.

Keywords Fluid therapy • Restricted fluid therapy • Liberal fluid therapy • Edema • Revised Starling equation and glycocalyx model (RSE&GM) • Colloid • Crystalloid • Resuscitation • Hypoalbuminemia

Key Points

1. While extreme fluid deprivation and fluid overdose resulting from negligence or misinformed prescription are undoubtedly harmful, observations and experiments do not point to fluid therapy as a significant determinant of patient outcomes from major surgery. Therapy maintaining fluid balance less than 2 l is probably optimal.
2. There are two interdependent fluid circulations (blood and interstitial fluid) serving the needs of cells and intracellular fluid.
3. Filtration rate (J_v) of fluid from the blood circulation to the interstitial circulation is a major determinant of the dynamic equilibrium between plasma volume and interstitial volume. It is affected by anesthesia and by vasoactive agents.

T.E. Woodcock, MB, BS, MPhil
Department of Critical Care, University Hospital Southampton, Southampton, UK
e-mail: tom.woodcock@me.com

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4. In hypovolemia, the plasma oncotic pressure has little or no effect on J_v; the common assertion that "colloids should be used to replace blood loss" is therefore a fallacy and the most dangerous of the many shibboleths found in current teaching of fluid therapy.
5. It is time to dispel the colloid delusion; observation and research indicate that the red cell dilution efficiency of colloid solutions is up to 5 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. Proponents of colloid therapy argue that leaky capillaries are a distinguishing feature of sepsis, and that colloids can continue to be used in nonseptic trauma and surgery cases. 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. While hypotonic solutions may be safe and rational for the maintenance of fasted subjects, the free water load cannot be cleared by arginine vasopressinemic patients whose renal collecting ducts are rendered permeable to water.

Introduction

> Remove far from me vanity and lies: give me neither poverty nor riches; feed me with food convenient for me. *Proverbs 30.8* King James Version (Pure Cambridge "Authorized Version")

It has long been believed 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]. 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, 9]. As we shall see, this paradigm is far 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. For many years I delivered the Royal College of Anaesthetists' Final Fellowship Course lectures in London on "Controlling the Circulation." It troubled me that the traditional teaching, which I dutifully delivered to the examination candidates, was largely irrational. Then, in 2010, I came across the review article that was a revelation to me [10]. The revised Starling principle, confirmed by experiments published in 2004, had been ignored by clinicians, and 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].

In 2012, my physiologist son and I offered what we believe to be a better paradigm, based on modern cardiovascular physiology as taught by J. Rodney Levick at St. Georges Hospital in London, to underpin a rational approach to fluid therapy [13]. We called it the revised Starling equation and glycocalyx model (RSE&GM) [14]. 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 [15, 16]? It explains why albumin bolus therapy is no more effective than isotonic salt solution in shock therapy, and why fluid boluses may be harmful [17, 18]. It explains why extravascular lung water may increase during fluid loading in the critically ill with presumed hypovolemia [19, 20].

A subsequent review of intravenous fluid therapy for adults now accepts our view that any intended effect of a hyperoncotic plasma reabsorbing interstitial fluid is unlikely as the majority of interstitial fluid is returned to the circulation via the lymphatic system, not by local microcirculatory reabsorption [21]. 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" [22]. Robert Hahn, who has published much research on the distribution of body fluids, had previously commented that "fluid therapy may be more complicated than you think" [23]. He now accepts that the glycocalyx model rules out reabsorption across continuous capillaries. He hypothesizes that the visco-elastic properties of the interstitial matrix may largely explain the fact that distribution of an infused isotonic salt solution is dependent on the rate of infusion [24]. In this chapter, I update the evidence supporting RSE&GM and consider how this paradigm aids truly rational prescribing.

Ludwig Wittgenstein and the Scientific Method in Medical Inquiry

Ludwig Wittgenstein is regarded as one of the greatest thinkers of the twentieth century. His most famous aphorism is perhaps the stark concluding statement of his *Tractatus*, "Whereof one cannot speak, thereof one must be silent." During the Second World War he left his post as a professor of philosophy at Cambridge University and worked as a technician with the Medical Research Council in 1942, investigating the condition known as wound shock with R. T. Grant at the Royal Victoria Infirmary in Newcastle upon Tyne. During this time he wrote no philosophy. He designed and built an improved device for the investigation of the relationship between breathing rate and volume and pulse rate and volume. He told a friend that "it is all very much more complicated than you would imagine at first sight." Wittgenstein was impressed by Grant's concern that research into shock was doomed to futility while the word "shock" remained an ill-defined and unusable concept. Their diatribe against the word shock led Wittgenstein to suggest the word be printed upside-down to emphasize its unusability [25]. Basil Reeve, another member of the research team, said he had learned two important things of relevance to medical inquiry from Wittgenstein. First, to bear in mind that things are as they are; and secondly to seek illuminating comparisons to get an understanding of how they are [25]. The lessons that Wittgenstein's philosophy offers to medical inquiry have yet to be fully appreciated [26].

The scientific method starts with the observation of how things are. To what extent are surgical complications caused by suboptimal fluid therapy? Do complications caused by suboptimal fluid therapy (excluding negligent failure to treat or willful overdose) lead 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 [27]. 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.

As we begin a discussion of liberal or restricted fluid therapy, Wittgenstein reminds us that we need definitions of the concepts. Varadhan and Lobo made a very

helpful contribution in 2010 in their meta-analysis of nine randomized controlled trials of intravenous fluid therapy in major elective open abdominal surgery [28]. 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. Zero-balance, or euvolemic goal-directed fluid therapy (GDFT), is increasingly seen as good perioperative practice [29].

Clinical Research

Doherty and Buggy reviewed the evidence on perioperative fluid therapy volumes up to 2012 [30]. 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 [31]. 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 [32]. 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 [33]. She then randomized 32 ASA 1–3 patients undergoing inpatient colonic surgery and found better postoperative arterial oxygenation with restrictive therapy [34]. 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 [35]. 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. In the contrasting clinical context of relatively low-risk patients undergoing ambulatory surgery, they are convinced that high-volume crystalloid infusion (20–30 ml/kg) reduces postoperative nausea and vomiting, dizziness, and pain [30]. 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 [36]. 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 withhold or 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 modern laparoscopic bariatric surgical practice over 1 year included 224 patients. Patients who received less than 1,750 ml of intraoperative fluids experienced longer hospital length of stay when compared to patients who received more than 1,750 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 [37].

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 [38]. 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 [39]. 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 [40].

At the time of writing (January 2016), an international multicenter randomized controlled trial called RELIEF (REstrictive versus LIbEral Fluid Therapy in Major Abdominal Surgery) is underway. Planned to recruit 2,800 patients over 3 years, it is hoped this will throw great light on this long-running debate. (http://www.relief.org.au/)

Biophysical Colloid Osmotic Therapy. Clinical Considerations

Ernest Starling's name is celebrated whenever critical care physicians discuss fluid therapy for hemodynamic resuscitation. The Frank-Starling Law of the heart still underpins perioperative hemodynamic therapies. Starling's principle of fluid exchange with the tissues, on the other hand, has been less successful in describing what we see in patient care. Starling himself recognized the limitations of his canine experiments. He indicated his reservations when he said that edema is *probably* absorbed directly by blood vessels, and that the colloid osmotic pressure of serum is *probably* responsible for absorption of isotonic fluid from the tissues to the

bloodstream, which ensues on any general lowering of capillary pressures [41]. During World War I, Starling and his brother-in-law William Maddock Bayliss, professor of general physiology at University College London, were called to sit on the "Special Investigation Committee on Surgical Shock and Allied Conditions" of the Medical Research Committee. Bayliss believed that intravenous therapy would be more effective if it included a substance to maintain the viscosity of the blood, and experimented with 5 % solutions of gelatine or gum acacia. He also noted that such solutions had a colloid osmotic pressure comparable to that of serum, and the concept of a biophysical treatment for shock was conceived. In 1917, Bayliss went to France, and many moribund soldiers were given a bottle of "gum saline" to observe its effects on "wound shock" [42]. Underpinned by an undisputed physiological principle, the rationale for biophysical colloid resuscitation was accepted around the world, and survived for a century. In anticipation of shock casualties during World War II, Harvard protein scientist Edwin Cohn developed the plasma fractionation process that bears his name and made albumin infusions available for battlefield resuscitation.

With the establishment of intensive care units and the diagnostic application of pulmonary artery pressures in the 1960s it became possible to stabilize and to study patients with shock [43]. The pulmonary artery flotation catheter was a particularly powerful tool for the investigation of the effects of colloids [44]. At the 1978 Hyland Symposium on pulmonary edema, Civetta explained how physiological considerations lead to the unexpected conclusion that oncotically active substances can only serve to enhance the formation of interstitial edema [45]. The following year, Virgilio presented data from surgical patients that "seriously question the necessity to maintain colloid osmotic pressure by using protein solutions during acute hemodynamic resuscitation" [46]. By 1983, Tranbaugh and Lewis were able to state firmly that analysis of the Starling microvascular forces operative in the lung did not provide a reason to prefer colloid resuscitation, and they had data confirming that crystalloids were both safe and effective. Of colloids, they said, "one wonders how their further use can be justified" [47]. The automation of the cold indocyanine green double-indicator dilution technique for the estimation of extravascular lung water provided an additional powerful bedside tool [48].

J. Rodney Levick challenged the standard teaching of transvascular filtration being balanced by transvascular absorption in a review article of 1991 [49]. Absorption, he argued, cannot be maintained across most low-pressure exchange segments because there is a rise in pericapillary interstitial colloid osmotic pressure as filtration slows and then ceases, keeping the transvascular colloid osmotic pressure difference smaller than the reduced hydrostatic pressure difference. The anesthesia and critical care community did not notice this remarkable revision of fluid physiology, which makes a biophysical osmotic therapy for resuscitation unlikely to be effective. In neonatal practice, Emery, Greenough, and Gamsu asked the pertinent question whether it is the dose of colloid (albumin) or the volume of the solution that achieves resuscitation. Their subjects, 60 hypotensive preterm infants, received their resuscitation fluid at 5 ml kg^{-1} h−1. Twenty received the full dose of colloid as 20 % human albumin solution delivered in 1 h, while 20 received plasma,

and 20 received 4.5 % human albumin solution 15 ml kg^{-1} h^{-1} over 3 h. The total dose of protein was therefore similar between groups, while the hyperoncotic albumin group received a smaller volume. The degree of resuscitation was similar in all three groups after 1 h, but after 3 h restoration of blood pressure was better in the higher-volume (15 ml kg^{-1}) groups. They thereby showed that it is the volume infused rather than the colloid load that is important in producing a sustained increase in blood pressure [50]. The next question was whether albumin was necessary at all, and it was answered in 1997 by So, Fok, Ng, and colleagues. Sixty-three hypotensive preterm neonates were treated with an infusion of either 5 % albumin or isotonic sodium chloride at 10 ml kg^{-1} h^{-1} until they were adequately resuscitated. Albumin did not reduce the volume of fluid required to achieve resuscitation, and it was associated with postresuscitation fluid retention, as predicted by Civetta 18 years earlier [51].

The colloid–crystalloid debate continued with the encouragement of the colloid industry. Another blow was dealt in 2004 by 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 [15]. Today we can interpret that as an example of colloid-induced anemia. 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]. Students must now familiarize themselves with the glycocalyx model, also known as the Michel–Weinbaum glycocalyx junction-break model of fluid exchange in a continuous capillary [13, 52]. Starling’s hypothesis that “absorption from the tissues…ensues on any general lowering of capillary pressures” does not occur, and biophysical colloid osmotic pressure therapy in resuscitation is no longer supported by physiological reason. 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 [53]. 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 [16]. 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” [54]. The Cochrane collaboration continues to advise that hydroxyethyl starch is nephrotoxic in all patient populations, so alternative therapies should be used [55]. They also advise that colloid solutions are at best nonsuperior to a crystalloid solution and are much more expensive [56]. There

are so little data on the modified fluid gelatins that we can have no confidence that they are safe to use [57]. While some anesthetists still feel incapable of managing surgical patients without biophysical osmotic therapy, the fact is: "Crystalloids will do the job in the operating room" [24].

A New Paradigm for the Prescription of Intravenous Fluid Therapy

The revised Starling equation and Glycocalyx model (RSE&GM) paradigm retires the view of colloids as preferred plasma substitutes and focuses instead on the central volume of distribution of an infused fluid, its rate of distribution to a peripheral volume, and its rate of excretion (Fig. 8.1). In short, it emphasizes volume kinetics. RSE&GM brings several recently described 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 presenting a clinician's simplified approximation of the relevant physiology, and do not claim to be an academic physiologist. An appreciation of vascular physiology as described in *An Introduction to Cardiovascular Physiology 5th Edition*, in particular chapters 9–11, is recommended [13].

The human microvasculature is composed of four very different types of capillaries, whose distinct functions must be appreciated [14]:

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 layer 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.
2. The highly specialized renal glomerular capillaries are continuous but feature fenestrations for the filtration of fluid to the renal tubules (the glomerular filtration rate [GFR]).
3. Diaphragm-fenestrated capillaries are specialized to absorb fluid from interstitium to plasma when needed, and 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 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 endothelial glycocalyx layer, while the area for fluid exchange is a function of the length of the slit-like junction breaks between

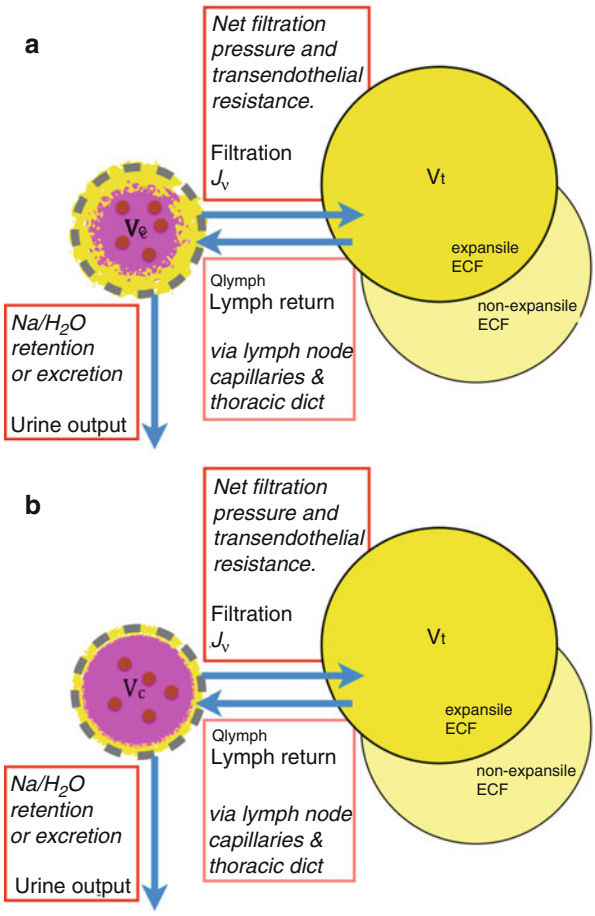

Fig. 8.1 A kinetic diagram of extracellular fluid distribution. Gel phase of the central and tissue volumes indicated by yellow, free-flowing plasma of the central volume indicated by pink. Erythrocyte volume indicated by red disks. (**a**) Shows a healthy intravascular gel phase (the endothelial glycocalyx 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

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 glycocalyx 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. It entraps and retains albumin molecules, 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 layer components including the GAGs appearing in blood samples. 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.

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 peripheral volume that broadly represents the intravascular and extravascular fluid volumes, respectively [58]. 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. 8.1). 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 whole extracellular fluid volume. In systemic capillary leak syndrome, so much fluid goes to the soft tissues of the limbs that it can cause compartment syndromes.

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. I propose that the third is the noncirculating intravascular volume occupied by the endothelial glycocalyx, which creates a fiber matrix scaffold for the endothelial surface layer (Fig. 8.1). Being on average about 2 microns thick, the fragile glycocalyx 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) of the endothelial glycocalyx layer will increase the volume available to red cells and lead to a reduction in the hematocrit. GAGs are 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 %" [59]. 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. 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 %" [59]. Erythrocyte or albumin dilution data were wrongly presumed to indicate resuscitative effectiveness. This error is still common among experts.

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(pi)g close to zero. The transendothelial colloid osmotic pressure difference delta π(pi) is then maximal, and further increases in delta P will widen the difference between delta P and the now-fixed delta π(pi), causing a sharp rise in J_v. This creates an inflection on the curve that makes it appear J-shaped (Fig. 8.2). The inflection is called the J-point.

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

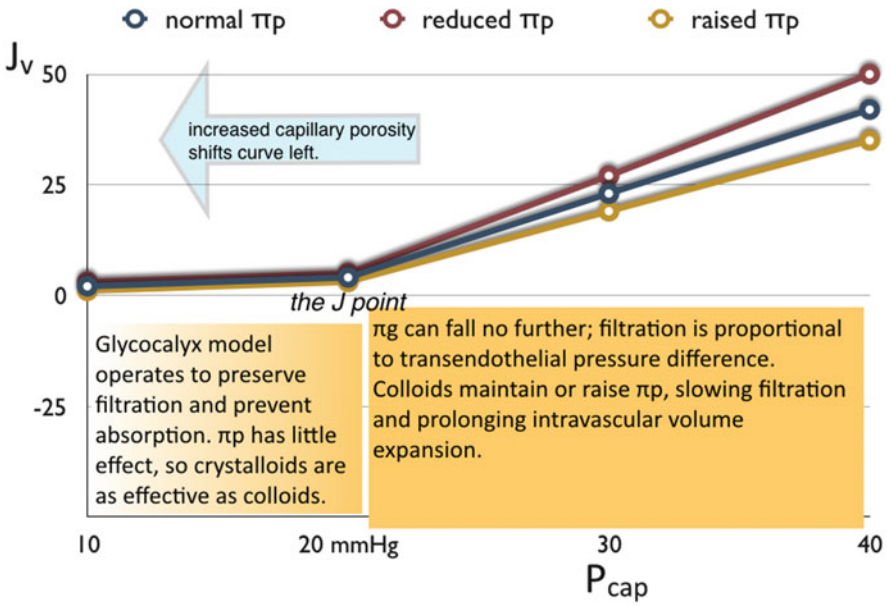

Fig. 8.2 The J-curve. A plot of the transendothelial solvent filtration rate J_v against the capillary pressure P_{cap}. In health, capillary pressure is regulated around the J-point. Raising the colloid osmotic pressure of plasma π(pi)p only increases the transendothelial colloid osmotic pressure difference delta π(pi) when capillary pressure is higher than normal (heart failure or fluid overload) and the sub-glycocalyx colloid osmotic pressure π(pi)g is close to zero. Around and below the J-point (health and hypovolemia), J_v is low and essentially uninfluenced by π(pi)p

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 is to maintain an adequate mean 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 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 [39]. They have even been found to increase urine output, but I do not think it is helpful to describe this as a diuretic effect [24].

Concern that capillary hypertension is injurious will make us more cautious about employing rapid boluses. 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. For illustrative comparison he asks us to imagine a rubber balloon that loses some elasticity once it has been overdistended. Hahn argues that if we can minimize distension of the space, we preserve its elasticity and preserve the tissue pressure that drives return of lymph to nodes and the thoracic duct. Edema is avoided, and the central fluid volume conserved, if we infuse fluids at lower rates [24].

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 Lp). 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) [60]. Bhave and Neilson speculate that short-term sodium storage and interstitial volume homeostasis may be relevant to transient or nonequilibrium phenomena such as blood pressure (BP) dipping, flash pulmonary edema, rapid blood loss, burns, and sepsis. 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(pi) to the effective delta π(pi). 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. Lee and Slutsky have reviewed the biology and potential for therapeutic manipulation of the proteins that zip adjacent endothelial cells together, or unzip them creating the junction breaks [61]. 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 recently reviewed understanding of the tonic regulation of vascular permeability in health and disease [62]. 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 reenters 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 adrenergic agents and suppressed by inflammatory mediators. 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.

Was Ernest Starling Wrong in the Interpretation of His Experiments?

Let us go full circle back to Starling's laboratory more than a century ago. He deduced the following:

1. Salt solutions, isotonic with the blood-plasma, can be and are absorbed directly by the blood vessels. This statement probably holds good for dropsical fluids containing small percentages of proteids.
2. A backward filtration into the vessels is mechanically impossible in the connective tissues of the limbs, of the muscles, and of the glands similar in structure to the submaxillary.

3. The proteids of serum have an osmotic pressure of about 30–40 mmHg. Absorption of isotonic salt solutions by the blood vessels is determined by this osmotic pressure of the serum proteids. The same factor is probably responsible for the absorption from the tissues that ensues on any general lowering of capillary pressures, for example, artificial anemia.
4. The proteids of the tissue fluids, when not used up in the tissues themselves, are probably absorbed mainly, if not exclusively, by the lymphatic system.

So he correctly concluded that injected isotonic salt solutions are absorbed directly by the blood vessels; it was only his hypothetical extrapolation of this finding to the absorption of "dropsical fluids" that was mistaken. How are they different? Consider the Michel–Weinbaum glycocalyx junction-break model of fluid exchange in a continuous capillary once more and see if you can find the reason for yourself before reading the following explanatory paragraph.

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. If you, not unreasonably, thought that raised interstitial pressure at the site of injection might reverse the hydrostatic filtration pressure difference, look again at Starling's second statement that "backward filtration is mechanically impossible."

Considerations for Current Practice

Which Fluids?

Physiology predicts there will be very little, if any, excretion of electrolyte-free water in many hospitalized patients, because the stress hormone arginine vasopressin makes the distal parts of the nephron 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. It is reported that fifth normal saline has been removed from some UK hospitals because of multiple episodes of fluid and electrolyte complications [21]. An editorial comment warned that "there can be no justification for administering hypotonic fluids in the

perioperative setting" [63]. Moritz warned anesthetists 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 [63]. 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 [64]. 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 [65]. This study was not noticed by UK experts who opined that "Lactated Ringer solution and normal saline are not maintenance solutions, because their sodium content is much too high" [66]. Moritz and I have criticized UK guidance, which unfortunately advocates fifth normal saline in glucose for postoperative fluid therapy [67, 68] 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 [69]. 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. A recent UK National Institute for Health and Clinical Excellence review found that evidence could not demonstrate whether hyperchloremia was more to be feared than hypochloremia, and it was not possible to determine whether abnormal serum chloride in either direction was a complication of fluid therapy rather than a symptom of the underlying disease [68, 70]. 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 [69]. 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 [71]. 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 recent 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 was not allowed, but a small postinduction bolus of up to 5 ml/kg could be administered if needed. Intraoperative maintenance fluid rate was 5 ml/kg/h. Postoperative maintenance was 40 ml/h, or 0.5 ml/kg/h for larger patients. Urine output to be maintained at 30 ml/h averaged over 4 h (i.e., 120 ml per 4 h). Their favored solution was Hartmann's, but other isotonic or near-isotonic solutions could be used. They also used colloid as their bolus fluid, though we now know that crystalloid is no less effective for delivering good outcomes without exposing the patient to nephrotoxic or allergenic colloids [40]. Moritz favors glucose 5% sodium chloride 0.9% for maintenance in acutely ill and major surgical patients, but for safety reasons this solution is very rarely used in adult practice in the United Kingdom [72]. Additional fluid could be prescribed to replace blood lost, for which 2 ml crystalloid per milliliter of blood should suffice in nonmajor hemorrhage, or to treat hypotension that did not respond to a vasopressor. 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 [29]. 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 [73].

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 [74]. Where it is available, normal saline in glucose may be preferable. Hartmann's solution increases glycemia and is probably best avoided in diabetics.

What Monitoring?

Consider first the strategy of 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 [75].

Brandstrup randomized 150 patients undergoing colorectal surgery to a zero-balance protocol or an optimal stroke volume protocol and found no difference in outcome [76]. Her fluid management involved hydroxyethyl starch in both treatment limbs. A Cochrane systematic review published in 2013 identified 31 studies involving 5,292 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 [77]. Later trials have supported their conclusion [38, 40]. Unsurprisingly, arterial pulse contour analysis did not improve outcomes for elderly spontaneously breathing patients under spinal anesthesia [78]. OPTIMISE enrolled 734 high-risk patients undergoing major gastrointestinal

surgery and could not demonstrate an advantage for hyperdynamic therapy [79]. By the sophistry of adding their data to a meta-analysis, they were able to claim a statistically significant reduction in the complication rate. 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.

The second strategy is 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 trauma, surgery, or sepsis [80, 81]. 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 [82–84]. 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. This evidence provides physiological reasons why bolus therapy was observed to be harmful in the Fluid Expansion As Supportive Therapy (FEAST) trial [17]. 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.

Alpha-1 Agonists

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. [59]. This is a controversial treatment as 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 ventricular preload. 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 preload [85]. 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 also increases urinary excretion, counteracting anesthesia-induced oliguria. Hahn notes that this dose does not noticeably slow heart rate or raise blood pressure, and does not reduce the plasma volume as might occur at a higher dose. He suggests that phenylephrine infusion could be considered as a diuretic and reduce the need for furosemide. 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 [39]. While we must caution that further research is needed, low-dose norepinephrine or phenylephrine infusion (or other alpha-1 agonist) is likely to be a useful tool in the anesthetist's armamentarium.

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Chapter 9
The Perioperative Use of Albumin

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.

Keywords Human serum albumin • Sepsis • Antioxidant • Nitric oxide • Neuroprotection • Endothelium glycocalyx

E. Farag, MD, FRCA (✉)
Professor of Anesthesiology, Cleveland Clinic Lerner College of Medicine, Director of Clinical Research, Staff Anesthesiologist, General Anesthesia and Outcomes Research, Cleveland Clinic, Cleveland, OH, USA
e-mail: farage@ccf.org

Z.Y. Ebrahim, MD
Department of General Anesthesiology, Anesthesiology Institute, Cleveland Clinic, Cleveland, OH, USA

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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. 9.1) [5].

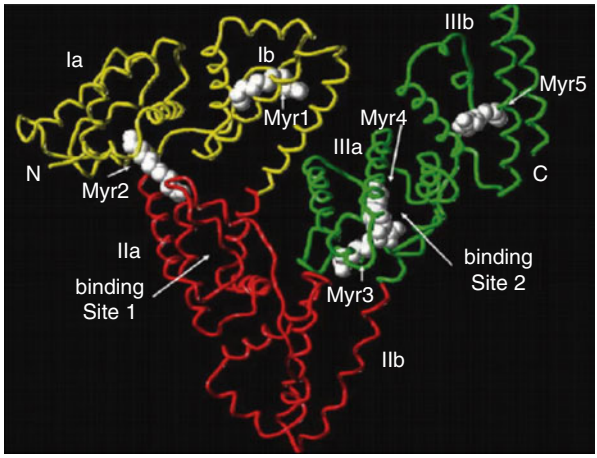

Fig. 9.1 X-ray structure of human serum albumin (Reprinted with permission from Kratz [81]. Proceedings of the Tenth European Symposium on Controlled Drug Delivery)

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 encodes a precursor protein (preproalbumin) of 609 amino acid residues. Cleavage of the single peptide of 18 residues and the propeptide (proalbumin) of six residues yields the mature protein of 585 residues [6].

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 [7–9]. 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 [10].

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 [11]. 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 [12]. 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 [13, 14].

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 ven-

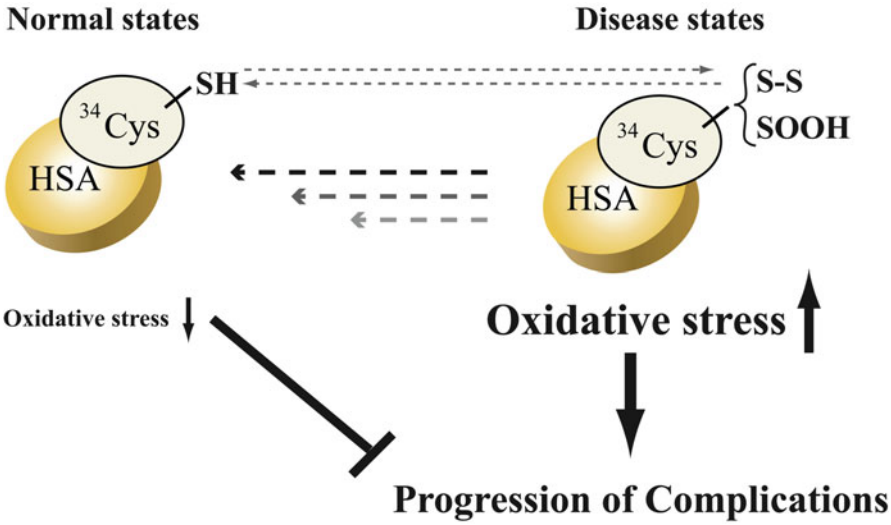

Fig. 9.2 Proposed mechanism for the contribution of Cys34 to the maintenance of homeostasis in blood. The treatments where the levels of Cys34 oxidation are minimized at low levels in several diseases may be beneficial for preventing the onset and progression of serious complications, which affects the prognosis for survival (Reprinted with permission from Anraku et al. [82])

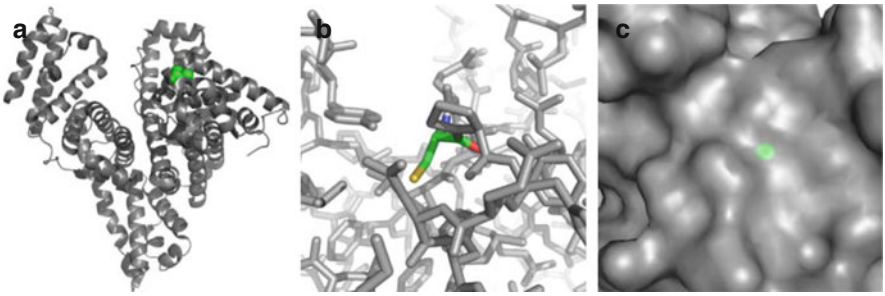

Fig. 9.3 Three-dimensional structure of human serum albumin, local environment, and surface exposure of Cys34. (**a**) Cys34 is shown in *green*. (**b**) Thiol microenvironment: C, *green*; O, *red*; N, *blue*; S, *yellow*. (**c**) Surface exposure of Cys34. Atomic coordinates were downloaded from Protein Data Bank, Accession Code 4EMX. The figures were prepared using PyMOL v0.99 (www.pymol.org) (Reprinted with permission from Turell et al. [83])

tricular myocytes against in situ–generated oxidative stress [15, 16]. 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. 9.2 and 9.3) [17].

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 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 [18]. 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 [13]. 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 μ[mu] M) 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 [19]. 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 [13]. Other RNS, such as peroxynitrite ($ONOO^-$), constitute powerful oxidants and nitrating species [20]. 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) [21, 22]. 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 [23]. Interestingly, West Nile virus is neutralized by hypochlorous acid-modified HSA that binds to domain III of the viral envelope protein E [24].

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 nonenzymatic 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 [25]. 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 [13].

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 [26]. Glycated albumin was shown to impair vascular endothelial NO synthase activity in vivo in aortas of rabbits [27]. 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 [28]. 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 [29].

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 antiaggregatory effects on platelets [30]. 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 not 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 [6, 13].

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 [31]. 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 [32]. 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 [33]. 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 [34].

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 [13]. In its long half-life of ~2–3 weeks, 1 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 [30]. 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 [30]. 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 β (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 [35–37].

The catabolism of HSA takes place in several organs at a rate of about 14 g per 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 [13].

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* [38]. 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 [39, 40]. Moreover, the meta-analysis did not include burns trials in which the mortality rate was lower in albumin [41]. 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 [40]. Only a few years later, this meta-analysis was followed by an updated meta-analysis, in which 55 trials involving 3,504 randomly assigned patients had been included and 525 deaths occurred [40]. 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 7,000 critically ill patients were published, showing that a 4 % albumin solution was as safe as normal saline as resuscitative fluid in critically ill patients [42]. 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 1,977 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 % (CI 95 % 0.67–1.0, $P = .047$) [1]. Caironi and colleagues randomized 1,818 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 (1,121 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; $P = 0.03$) [43]. 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 [44]. Furthermore, the improved survival associated with albumin in patients with septic shock was confirmed in a recent meta-analysis. In this meta-analysis, 3,658 with severe sepsis and 2,180 with septic shock patients were included in the analysis [45]. 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; $P = 0.03$) [45].

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 [46]. 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 [47, 48]. In patients with acute respiratory distress syndrome, the use of albumin improved oxygenation but did not affect mortality [49].

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 [50].

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 [51]. 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 [51]. 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 [51].

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 [52]. 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 [53].

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 [54]. 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 [55, 56].

The mechanisms of the neuroprotective effects of albumin could be explained by its ability to attenuate brain edema and inhibit the endothelia cell apoptosis [57, 58]. Albumin administration may improve microcirculatory blood flow, increase organ perfusion, decrease leukocyte rolling and adherence, and reduce the inflammatory response [59]. 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 [53]. 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 [13]. 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 [53].

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 [60, 61]. 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 [62]. Therefore, the correct conclusion should be hypo-osmolar solutions should not be used in patients with TBI [63].

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 [64].

Oliver et al. compared 5% albumin priming with fresh frozen plasma (FFP)-based priming in pediatric patients [65]. 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 [66].

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 [67]. 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 [68]. 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 [69]. 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 [70]. 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 [71, 72].

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 [73]. 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 [74].

Currently available human albumin solutions may differ in protein content and composition, binding capacity, metal ion content, antioxidants prosperities, and capacity to bind drugs [75]. 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 [76], which may influence the properties and hence the clinical impact of albumin solutions [77].

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 %) [78]. Hypertonic albumin (20–25 %) is used in patients with edema as it avoids excessive sodium and chloride loads [75]. 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. 9.4) [79, 80].

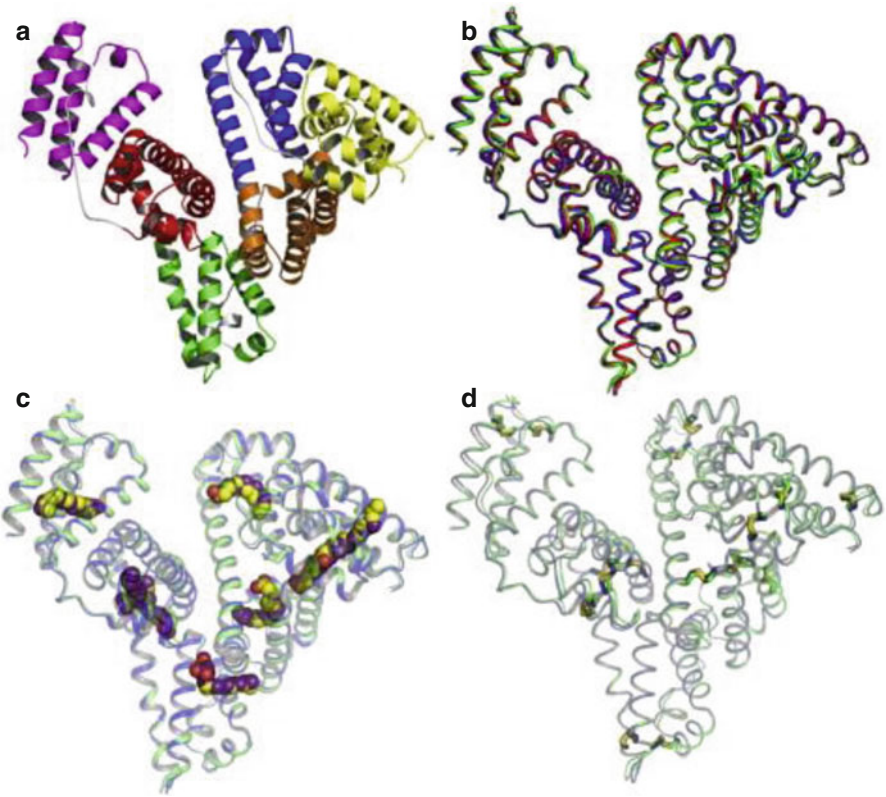

Fig. 9.4 Structures of rHSA from yeast and rice. (**a**) Overall structure of recombinant human serum albumin. (**b**) Comparison of recombinant HSA from rice (*green*, PDB: 3SQJ) or yeast (*blue*, PDB: 1E7G) to HSA from plasma (*red*, PDB: 2I2Z), the RMSDs of two rHSAs to pHSA were 0.605 and 0.374 Å, 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. [79])

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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Chapter 10
The Dilemma for Using Hydroxyethyl Starch Solutions for Perioperative Fluid Management

Christiane S. Hartog and Konrad Reinhart

Abstract Hydroxyethyl starch is a colloid plasma expander that has recently been reviewed by the European Medicines Agency (EMA) following safety concerns in critically ill patients or in patients with sepsis. The EMA decided to restrict 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. 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.

Keywords Colloids • Crystalloids • Fluid therapy • Mortality • Renal failure • Coagulopathy • Pruritus • Patient safety • Adverse effects

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.

C.S. Hartog, MD (✉) • K. Reinhart, MD
Department of Anesthesiology and Intensive Care Medicine and Center for Sepsis Control and Care, Jena University Hospital, Jena, Germany
e-mail: Christiane.Hartog@med.uni-jena.de

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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. On December 19, 2013, the European Commission implemented a decision 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 10.1) [1].

Box 10.1 Restrictions to HES use issued by EMA 2013
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.

The European Commission also issued contraindications and warnings for the use of HES outside the intensive care unit (ICU) (Box 10.2). 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]. These recommendations of 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 and published a divergent statement.

They concluded that suspension of marketing authorization in all patient populations was appropriate to protect public health, 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 10.2) [2].

Box 10.2 Divergent Statement by the EMA PRAC Committee
Divergent Statement by the EMA PRAC Committee [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 three- to fourfold, 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 per 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

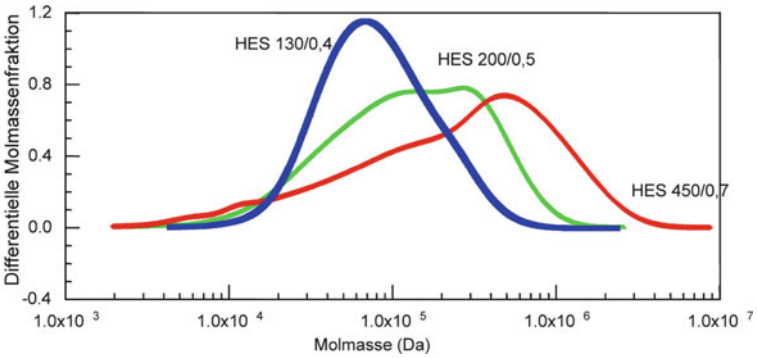

Fig. 10.1 Molecular size distribution in serum of rats after application of different HES solutions. This figure shows the distribution of molecular size in different HES solutions. All HES solutions are polydisperse and contain molecules of different sizes. The *x*-axis shows the molecular weights in Daltons, the *y*-axis shows the differential fraction of molecular sizes among each solution (Reprinted with permission from Wagenblast [16])

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 hydroxyethlation 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. As Fig. 10.1 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 kD) and 24.6 % (CI 17.8, 31.4) for high-molecular-weight HES (>200 kD) [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. They 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. 10.2) [14, 39–45]. Thus, the volume-sparing effect of colloids is considerably lower than believed. A 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].

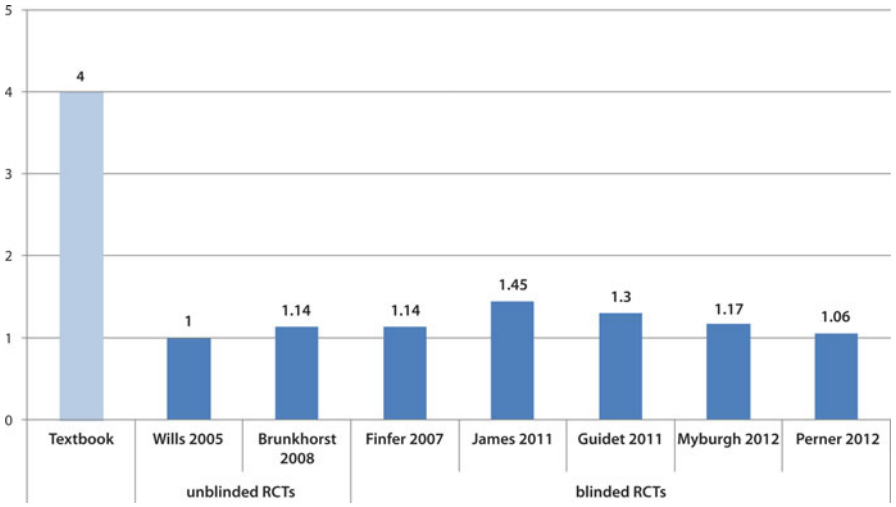

Fig. 10.2 Crystalloid-to-colloid ratios. While textbook knowledge based on theoretical arguments postulates a crystalloid-to-colloid ratio of 4 or higher, recent RCTs, among them five where study personnel were blinded to the nature of the administered fluid, found ratios between 1 and 1.45. The *y*-axis shows the ratio of crystalloid-to-colloid volumes that were administered to achieve preset hemodynamic endpoints in the respective studies [14, 39–45]

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 2,137 patients in the HES period and 2,017 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 7,000 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].

Hydroxyethyl Starch Toxicity

Like other synthetic colloids, HES is associated with a range of adverse effects [54]. 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 7,000 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 9,258 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].

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 % HES130/0.42 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 HES130/0.42 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].

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, 9,857 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, 8,402 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 ($\geq$ 200 kDa and >0.4 DS vs. 130 kDa and 0.4 DS) HES solutions, or high- versus low-dose treatments (i.e., $\geq$ 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 9,258 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 suggestion from small studies that HES may also impair kidney function in these patients. 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 6,478 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 4,409 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 7,000 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 7,000 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 kD) HES and finally included a total of 13 RCTs involving 1,156 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. 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 10.2) [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 other critically ill patients, nor were there any new studies in such patients to justify the revised decision. Moreover, treating acute blood loss in surgical and trauma patients with a substance that increases coagulopathy 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 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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Chapter 11
Balanced Versus Unbalanced Salt Solutions in the Perioperative Period

Sheldon Magder

Abstract Unlike organic electrolytes, elements in the blood, such as sodium (Na^+) and chloride (Cl^-), cannot be metabolized and their concentrations thus are dependent upon absorption and excretion. The concentration of Cl^- is on average 40 meq/L less than the concentration of Na^+ and this is an important determinant of hydrogen ion (H^+) concentration in blood (i.e., pH). Increasing Cl^- concentration produces acidemia and potentially affects renal, gastrointestinal, immune, and coagulation functions. There, thus, has been increasing interest in the use of intravenous solutions that have lower Cl^- concentrations. These solutions require anions besides Cl^- to "balance" the charge from Na^+. The major anions 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. Three large observational studies demonstrated potential benefits of low Cl^- solutions on renal function. There also has been suggestions of benefits for hospital survival and reduction of infections. This was not supported by the recent only reasonable-sized randomized clinical trial to test causality. However, the amount of fluid given was not large and the population was generally at low risk, thus limiting the power of the study to detect harm. Thus, the question remains unanswered in patients who are at higher risk. 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 endpoints 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.

Keywords Hyperchloremia • Sodium ion • Strong ion difference • Lactate • Bicarbonate • Acetate • Hydrogen ion • pH • Intravenous fluids • Osmolality

S. Magder, MD
Department of Medicine and Physiology, Critical Care Division, McGill University Health Centre, Royal Victoria Hospital, Montreal, QC, Canada
e-mail: sheldon.magder@muhc.mcgill.ca

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Key Points

1. To understand the potential harm from hyperchloremic acidosis it is necessary to understand the physiological and chemical implications of elements in body solutions.
2. Sodium (Na^+) is the major element for regulation of osmolality and chloride (Cl^-) is the major element for physiological regulation of hydrogen (H^+) in the body.
3. 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.
4. Future studies need to target high-risk patients including those receiving large volumes and those with underlying renal tubular dysfunction such as diabetics.
5. Endpoints should focus on renal, gastrointestinal dysfunction, infectious, and hematological adverse events.
6. Distinction needs to be made between the concentration of Cl^- and total body Cl^-.

Introduction

There is increasing interest in use of balanced salt solutions for fluid maintenance and resuscitation in critically ill patients [1–5]. This discussion begins with what it means when a solution is "balanced." I will then discuss the physiological roles played by the atomic elements in normal bodily fluids of all species with an emphasis on evolutionary importance of these elements. 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, although from the start it should be noted that there is limited useful clinical information. A central thesis of this chapter is that future clinical studies need to take into account the underlying physiological actions of the components of infused fluids and these studies will need to be targeted to potential pathological consequences of excess total body Cl^-. Some of these ideas have been previously reviewed [5, 6].

What Is a Balanced Salt Solution?

The 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 come out high on the list of sites as well as solutions for culturing cells. From a

Table 11.1 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

practical point of view, in contrast to the simple isotonic "normal" (0.9 %) saline solution, balanced salt solutions contain elements besides sodium (Na^+) and chloride (Cl^-) as well as inorganic molecules normally found in bodily fluids. Accordingly, these solutions also are called physiological fluids (Table 11.1). 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 that are dissolved in the solution. The energy produced by being in solution creates the major force that regulates the amount of water in the body. As a point of clarification, it is not the molar concentration of the substance that counts but rather its activity, because at higher concentrations there are interactions among components of the solution and the force is less than predicted just from the concentration. The activity is related to what are called equivalents per liter (Eq/L) and this unit will be used for concentrations throughout this paper. One milliosmole creates a pressure of 19.3 mmHg.

Osmolar force is related to the molar concentration of the substance and not the size of the substance. Thus, an element such as Na^+ has the same osmotic effect as a large albumin molecule. Because elements cannot be metabolized their concentrations in organisms can only be altered by absorption or excretion. Thus, sodium (Na^+), Cl^-, potassium (K^+), calcium (Ca^{2+}), and magnesium (Mg^{2+}) have key roles in

regulating the osmolality of bodily solutions. Elements can move down concentration gradients and water moves from areas of low concentration to areas of high concentration of electrolytes by moving across membranes. This is the basis of what is called the principle of iso-osmolality, which states that the all bodily compartments have approximately the same osmolality [9].

Current seawater is approximately 3 % salt, but when life began the salt concentration of seawater was 1 %, and this remains the salt concentration in the fluids of all organisms. It was important during evolution to maintain this osmolality because the solubility of the components of solutions and the tertiary structures of large molecules is much affected by a solution's osmolality. Thus, as the design of organic molecules became more complex it was necessary to conserve fluid osmolality from an initial evolutionary stage.

Initial cells were suspended in the sea and could readily exchange fluid and electrolytes across the cell membrane [10]. However, this would have limited cells to living in areas with large volumes of water at relatively constant concentrations. Without mechanisms to regulate the intracellular osmolality, early 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 with imbedded proteins for regulating intracellular metabolism, cell volume would have needed to be tightly regulated to avoid damaging these proteins tethered in the lipid membrane. Regulation of cell volume would have become even more important when the organism became multicellular because the increased diffusion distance would have created differences between cells at the center 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 the sea or the interstitial space. K^+ is situated below Na^+ in the periodic table and thus its properties are close to those of Na^+. K^+ also is the sixth most common element in seawater. 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 organisms, the extracellular space, too, could be protected from the outside by decreasing diffusion across an outer membrane and regulating the absorption and excretion of fluid through designated intake system (gastrointestinal tract) and excretory pathways.

The development of specialized membrane proteins that maintain differences in the intracellular and extracellular concentrations of K^+ and Na^+ provided two important forces that could be harnessed to regulate intracellular functions [11–13]. The concentration difference of electrolytes inside and outside cells created a force for diffusion that 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 [14, 15].

A fundamental principle for solutions with charged substances is the principle of electrical neutrality, which states 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. Regulation of Na^+ concentration has evolved as the primary process for regulating the amount of water in organisms [17], although changes in Cl^- can have some effects on water balance [18–20]. 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 and follows the concentration of Na^+ in order to keep the same intracellular osmolality as in the extracellular space. For this reason, calculations of total body water deficits or excess can be made just based on the concentration of serum Na^+ [21, 22].

Why Is the Concentration of Cl^- Less Than the Concentration of Na^+?

Cl^- has the greatest mass of all elements in seawater and the concentrations of Na^+ and Cl^- are similar, so why did the serum concentrations Cl^- evolve to be lower than that of Na^+? First, there is the practical point that other negative charges need to be accounted for. There are two major ones [16]. The first is bicarbonate (HCO_3^-), which is a dissociation product of carbon dioxide (CO_2), a major by-product of oxygen metabolism. HCO_3^- contributes about 25 mEq/L. The second is the ionic forms of dissociated proteins in blood. The dominant protein anion in plasma is albumin and it normally contributes between 16 and 17 mEq/L of charge. The second value from a biological point of view to having 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

Hydrogen ion (H^+) is unique among elements [23]. Because its core is only a single proton it has the highest charge concentration of any atom. Its strong electrical field affects any molecules around it and thus a change in its concentration can alter the tertiary structure of large proteins and nucleic acids and 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 [24]. 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 negative ions, such as Cl^-, are stronger than the concentrations of strong positive ions, such as Na^+, the negative charge difference must be

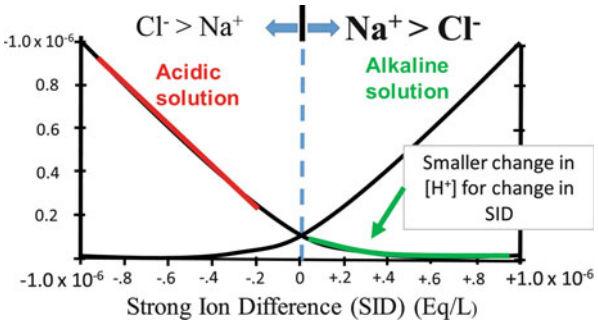

Fig. 11.1 Change in H^+ and OH^- with change in concentration of Na^+ relative to Cl^- (strong ion difference [SID]). When the SID is negative, changes in Cl^- match changes in H^+, but when SID is positive, changes in H^+ are much smaller than changes in Cl^- (or Na^+). The solution is also alkaline, 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 is 40×10^{-3} (millimolar) and not seen on this scale

matched by altering the dissociation balance of weaker substances. In a solution with only Na+and Cl^- in water, the only substance that can dissociate is water; H_2O to H^+ and OH^- and H^+ must balance the strong negatively charged Cl^- [16, 25] (Fig. 11.1). Under this condition, a change in the difference in concentrations of Na^+ and Cl^- must be matched one-to-one with a change in H^+ and the solution becomes more or 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 [25]. Importantly, this means that there is a much smaller change in H^+ with changes in the concentration difference of strong positive and negative ions. Thus, by having alkaline bodily solutions the effect of changes in the concentration of strong ions in bodily solution on H^+ is greatly modified and this provides a stabilizing effect on cell structures that are impacted by changes in H^+ concentration.

Based on the prior discussion, 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^- be lower than that of Na^+ and creates an acid–base balance that actually is not neutral but alkaline. It is important to understand that the pH of the solution is irrelevant for plasma pH because the plasma pH is determined by the final concentration of its components.

Balance in the Body

Almost all discussions around the potential benefit of balanced salt solutions revolve around the effect of these solutions on the composition of electrolytes in plasma (Fig. 11.2), because this is what can be sampled. Furthermore, elements in

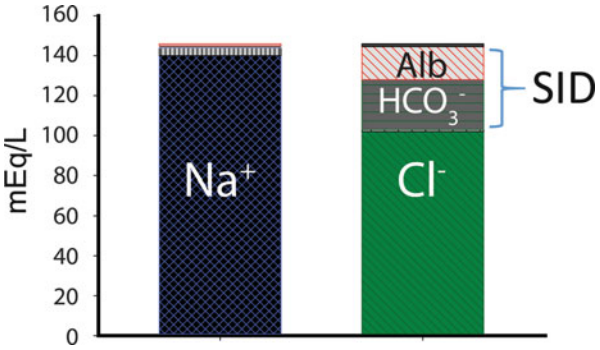

Fig. 11.2 Major electrolytes in normal plasma. The difference between strong positives primarily Na^+, and negatives, primarily Cl^-, is the strong ion difference and is primarily accounted for in plasma by the anionic form of albumin (*Alb*) and bicarbonate (HCO_3^-)

plasma are in equilibrium with those in the interstitial space except for minor deviations due to the greater concentration of proteins in plasma than in the interstitial compartment and what is called the Gibbs-Donnan equilibrium [9]. 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. The composition of negatively charged substances inside cells also is very different from the extracellular space. The difference between strong positives and strong negatives (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 [26]. 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: their Cl^- is 52 mEq/L, protein concentration is much lower than in other cells, and their SID is around 57 mEq/L [16, 25].

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 also can 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. Empirical 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. It needs to be emphasized that H^+ concentration in each compartment – that is, vascular space, interstitial space, or individual cells – is determined by the composition of electrolytes in that compartment. H^+ concentration in each compartment only changes if the balance of strong ions is changed by their movement into or out of the compartment or 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 outside of cell membranes [27] and trigger intracellular events, in which case the concentration will

matter; but because the Cl^- concentration inside cells is normally small relative to plasma, events inside cells could be affected more by the total amount of Cl^- in the body [28, 29]. Thus, increased total body Cl^- could have effects on cell function even when the Cl^- concentration in plasma is normal and may be more important than the plasma concentration. As examples, increasing the intracellular concentration of Cl^- in platelets increased epinephrine-induced aggregation through the alpha2-adrenergic receptor. Increasing intracellular concentration of Cl^- in vascular smooth muscle increased their contractility [30]. Lowering of intracellular Cl^- concentration is required for tumor-necrosis-induced activation of beta-2 integrins [31].

How Is the Difference Between Na+ and Cl^- in Blood Regulated?

As already indicated, the amount of atomic elemental substances in the body is determined by the amount taken in and the amount excreted for they cannot be metabolized. Infusion of salt solutions directly into blood is obviously very unphysiological for current organisms, although this was not the case for early organisms in which fluids could move across cell membranes directly into cells [10]. Our intake of Na^+ and Cl^- comes through the gastrointestinal tract, which has many mechanisms to selectively absorb electrolytes with a ratio of Na^+ and Cl^- that is different from what is taken in by the mouth [32–34]. A good example is the stomach, which in the fasting state secretes a very acidic solution that mainly has Cl^- as the strong electrolyte. It is often not appreciated that daily intake of water through the gastrointestinal tract is in the range of 2 L but the gastrointestinal tract secretes back into the lumen 8–10 L, which then is almost completely reabsorbed and in the process can contribute to the regulation of electrolytes [32]. This regulatory mechanism likely is significantly reduced when patients are not fed.

Intake of solutions with ionic contents that are higher than normal body osmolality will inevitably lead to dehydration and hypernatremia unless there is intake of free water. Attempting to drink a solution with high salt content, such as seawater, usually induces gagging 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 1,200 and 1,500 mMol of Na^+ [35]. His initial Na^+ was 209 mEq/L and 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 [36]. 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 ours. 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 seawater. The major regulation of the balance of the body's elements and osmolality fall to the kidney, which is discussed next.

Kidney: This remarkable organ when functioning normally 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^- [10]. The small difference in the reabsorption of Na^+ compared to Cl^- creates the 40 mMol difference between Na^+ and Na^+ 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 Cl^- in renal tubules. It also has to 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 [10, 37]. NH_3 itself has no charge and so it does not affect H^+ concentration, but at body pH it readily binds H^+ to form NH_4^+, which acts as a strong cation. The enzymes that produce NH_3 in the kidney are decreased or even lost when there is renal tubular dysfunction [38]. Excretion of excess Cl^- thus is much slower than excretion of Na^+. Initially, it largely involves excretion of excess K^+, which must be restored by increased intake or else serum K^+ can become very rapidly depleted and will lead to death [10]. Some Na^+ also is excreted, which can lead to significant volume depletion as indicated in studies in which patients with nephritis were given loading doses of CaCl [10, 39]. These physiological arguments support my earlier contention 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 stresses the renal tubular capacity to produce $NH4^+$ or the need to use other essential positive electrolytes.

As indicated earlier, 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 are important organs to study when determining the potential toxicity of high Cl^- loads. Endothelial cells, vascular smooth muscle [30], and blood cells [30, 31] 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 [27, 28, 40]. However, one must be cautious in interpreting these studies for the solutions used to increase the Cl^- load most often also 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 [40].

This is likely 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 the cell 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 [40]. 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 if NH_4Cl is used instead of NaCl. Prior volume depletion increases the response. Elegant studies on isolated afferent renal arterioles indicated that extracellular Cl^- modulates K^+ induced contractions through a Ca^{2+}-dependent process, but in the study approximately 30 % of vessels did not respond [27]. 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 is dependent upon volume status, glomerular function to 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 (Baxter Healthcare Corp., Deerfield, Il, USA), was studied in normal subjects who had no fluid overnight. The NaCl solution produced greater weight gain than the balanced solution. The difference in excreted volume was based on interstitial and not the plasma volume. As expected, serum Cl^- was higher, strong ion difference was higher, and bicarbonate concentration was 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 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, which as indicated previously, modulate renal responses to Cl^- [41].

Balanced Salt and Gut Function

The large secretory function of the gut makes it 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 absorptive processes and these have to

be blocked to identify Cl^- secretion [42]. Presumably, jejunal cells are better designed to be protective on the luminal side, for nature likely has not had to evolve 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) [43]. 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 paracellular 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 affect Cl^- handling by the intestine. 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, and solutions are given intravenously 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 [44].

The effect of balanced salt solution 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 [46]. The population was again very small; three groups of 30 were given 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 in 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) [47, 48] and CO_2/HCO_3^-, which has an effective pKa of 6.3. If CO_2/HCO_3^- were the only other substance 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 [25]. 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 (Fig. 11.3). 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 [4]. $CO_2/HCO3^-$ also cannot be mixed with a solution that has Ca^{2+} or Mg^{2+} for it could

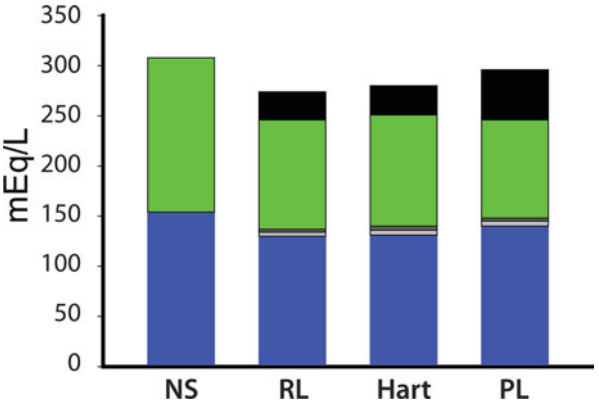

Fig. 11.3 Graphic composition of four commonly used intravenous solutions. *NS* normal saline, *RL* lactated Ringer's, *Hart* Hartman's, *Pl* Plasma-Lyte 148. The peak of the bar indicates the osmolarity. The *black region* indicates anions added to compensate for Cl^-

precipitate out as salts. An effective high-HCO_3^- short-term solution can be created by adding 3 ampoules of $NaHCO_3$ to 5 % dextrose in water, which effectively 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 nondissociated 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 centers 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 [25], which makes it look like HCO_3^- is moving up and then down its concentration gradient. What is actually happening is that 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 HCO_3^- production with the infusion of substances are done with controlled or spontaneous breathing. Although there is extensive discussion of bicarbonate secretion by the kidney [10], 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 and has little impact on CO_2 clearance. This is evident by the lack of increases in CO_2 patients without kidneys. If anything, total CO_2 goes down because the metabolic acidosis increases ventilatory drive. It also has been shown that acetate, succinate, and lactate salts can increase serum bicarbonate in dogs in which renal arteries are ligated [49].

Commercial balanced salt solutions use the moderately strong organic acids lactate, acetate, and gluconate to replace Cl^-. These all have pKa in the range of 3–4 and thus are almost completely in dissociated forms 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 for, as is the case with NaCl, they narrow the strong ion difference. However, they are quickly metabolized, primarily to CO_2 and water, and are alkalinizing because they leave behind Na^+, which is metabolized and widens 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 $NaHCO_3$ or gluconate-based solutions. The rationale was that gluconate is not readily metabolized but rather excreted with Na^+ and thus unlike the $NaHCO_3$ solution, there is no change in the SID and no alkalinization 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 can 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, for 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 indicates that there is a major pathological process [5, 52]. For example, in a person with 12 L of extracellular, 1 L of lactated Ringer's solution with a lactate concentration of 28 mEq/L, and no metabolism of the lactate would raise the plasma concentration by 0.4 mEq/L. Importantly, lactate is used by muscles and the heart as a fuel [53]; if there is not a process that is pathologically increasing lactate or no major liver failure, the relatively small 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, 55]. This was confirmed in a number of studies, which showed that, if anything, serum K^+ rose more with 0.9 % saline [56, 57]. There is evidence in isolated kidneys that lactate increases K^+ excretion [58]. K^+ also fell when sodium lactate was infused in dogs without renal function, indicating that this is likely due to intracellular shifts [49].

Acetate

Acetate is rapidly metabolized in blood and increases the concentrations of HCO_3^- more than lactate or succinate salts [49, 59]. Acetate in dialysate solutions are known to produce vasodilatation [60] and it was suggested that it also depresses cardiac function [61, 62]; but in a study comparing acetate to HCO_3^--based dialysate, acetate infusion actually increased cardiac function when assessed by echocardiography in humans [63] as well as in dogs [60]. In another study, the effect of acetate on blood pressure was no different from that of a bicarbonate-based solution [64].

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 [49, 50]. In the absence of renal function, acetate increased K^+ [49]. 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 glutamate was compared to bicarbonate-based solution as a primer for the bypass circuit for cardiac surgery patients [65]. Of note, glutamate can result in a false-positive galactomannan assay [66].

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 [49]. 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. There is a succinylated gelantin product (Gelofusine®, B Braun Medical, Melsungen, Germany) but this should not be confused with a balanced solution because 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 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 Ringer's (Isoplex®, Beacon Pharmaceuticals, Tunbridge Wells, UK).

Pyruvate is another anion that could balance Na^+ but it is toxic unless the enolate ethyl-pyruvate is formed [67]. This latter substance has anti-inflammatory and oxygen radical scavenging properties and was being evaluated for intravenous fluids use [68]. However, it failed to show any benefit in a stage II trial in patients

undergoing cardiopulmonary bypass [69]. 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 [70, 71].

Clinical Outcome Studies

There is a lack of properly designed randomized large clinical trials on the value of using balanced salt solutions for maintenance fluid management or resuscitation. This is very evident in the Cochrane analysis, which only managed to collect 11 randomized trials with mortality as an endpoint and only a few studies with other meaningful endpoints. All studies were hopelessly underpowered. There were only 267 subjects in the mortality analysis when it is likely that more like 10,000 are needed. 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 on 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 at the time of the report. However, there have been three large observational studies that provide some useful insights, and in 2015 a large cluster randomized trial was published.

Observational Studies

Three large and important studies are presented in historical order:

Shaw et al. analyzed a data set from almost a half million subjects who had undergone an open abdominal surgical procedure [72]. 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 Healthcare Corp., Deerfield, Il, USA) on the day of surgery. There were differences in the two groups. Patients who received the balanced salt solution were more likely to have private insurance and to be managed in large teaching hospitals indicating differences in socioeconomic class. To try to control for selection bias, the authors developed a propensity score for use of a balanced salt solution and used it to select patients from the saline group to match the Plasma-Lyte group. The major observations were that the saline group had more postoperative 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 these. The use of more blood tests is likely a real phenomenon because the higher Cl^- solution usually produces a negative base excess that likely triggers further blood tests from those who are naïve to the concept. This could be managed by increasing awareness of the expected electrolyte changes with use of only 0.9 % saline solutions. The increased infection rate remains an interesting question that is worthwhile pursuing considering the study discussed previously that showed that a higher Cl^- concentration reduces activation of beta-2 integrins in neutrophils [31].

Yunos et al. performed a sequential period pilot study at a single center with a little over 750 patients per period [73]. During 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 washout 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 the diminished Cl^- solutions was continued. The mean Cl^- infused decreased from 694 to 496 mMol/patient. In the control group, this would be the equivalent of 4.6 L of normal saline. The intervention resulted in less renal injury, less renal failure, and less use of 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 is 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 predefined 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 noncardiac surgery and whether the hyperchloremia was associated with length of hospital stay, morbidity, or 30-day mortality [74]. 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 analyze this possibility, these authors, too, performed a propensity analysis in which they assigned risk factors for developing hyperchloremia. These factors included sex, emergent surgery, last preoperative hemoglobin, main service of the operative procedure, procedure time, and minimum hemoglobin on postoperative day 1. Patients at risk for hyperchloremia were indeed sicker than those without. However, even within this higher risk group there were still more deaths, a longer length of stay in hospital, and greater incidence of renal risk in those who actually developed hyperchloremia than those who did not. Since this is not a controlled intervention trial, the higher incidence of events could still be because of some other factors for which they did not control. For example, they did not control for diabetes, which frequently is associated with renal tubular dysfunction and increased Cl^- but would be a risk in and of itself. There also was no record of how much fluid was given and of what type, so

it is not possible from these data to separate the effect of the plasma concentration of Cl^- and from the effect of the total amount given. They unfortunately did not comment on the incidence of infections in the two groups and bleeding.

SPLIT Study

The recently published SPLIT study is the first large randomized study to compare 0.9% saline to a balanced salt solution [75], although the authors still consider it a pilot study for it was underpowered to look at mortality as an endpoint. In this study, 2,278 patients were enrolled in a double-blind cluster randomized crossover design in four hospitals. Each hospital used the assigned fluids for 7-week periods two times during the study. There was no protocol for the amount of fluid given. The primary endpoint was a doubling of serum creatinine or a level greater than 3.96 mg/dL with an increase of ≥0.5 mg/dL from baseline. There were no differences in the primary endpoints or use of renal replacement therapy between the two groups. There was no significant mortality difference between treatments, but if anything the relative risk of death favored the saline group (saline 7.6% and balanced salt solution 8.6%). It would seem from this well done and large trial compared to any previous trials that there is no advantage to the use of balanced salt solutions. However, I believe that this conclusion is premature and what this study really tells us is how future studies should not be done. Many of these issues were very well covered in the excellent accompanying editorial by Kellum and Shaw [2]. The most important relate back to issues that I raised earlier about the potential pathophysiology of an excess of Cl^-. One important question that this study does not address is whether it is the serum concentration of Cl^- or total amount of Cl^- in the body that determines toxicity, because the concentration of Cl^- was not reported. Furthermore, the average volume given only was 2 L and it was given in 24 h. Thus, the total load was not high and much lower than in the Yunos study [73]. A second important factor is the ability of the kidney to excrete Cl^- as was shown by McClusky et al. who were able to identify subjects at higher risk for hyperchloremia [74]. In this study, the percent of patients with comorbidities was low. The percent with diabetes is not reported. Baseline creatinine values were in the normal range and similar in both groups. In summary, this was a relatively low-risk group who received a moderate amount of fluid. What can be concluded from this study 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 postoperative patients and infection rates were not assessed. The study gives no indication of potential effects in higher risk patients.

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 from use of Cl^--rich solutions, but as is the case for all observational studies they contain biases that 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, the one large randomized trial, 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 chloride solutions. The important question of bowel function after surgery also has not been adequately addressed in any study. The increased risk of postoperative infections in the study by Shaw et al. [72] should also be included in future randomized studies. I see little value in answering these questions with further database 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 bowel function postoperatively, infection rates, and renal function – and will require sample sizes likely in the 5,000–10,000 range. Death as an endpoint would likely require an even larger sample size, which would not permit collection of a rich enough clinical data set. Perhaps one group that could be studied with a smaller sample size is subjects who are expected to have a longer stay in the intensive care unit (ICU) and thus will be exposed to a higher load of Cl^-.

Clinical Considerations in the Perioperative Period

The physiological rationale 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 only prospective randomized study that addressed causation showed no benefit. On the other hand, failure to demonstrate a lack of benefit does not mean that there is no benefit and as I have already noted, I do not believe that the SPLIT study [75] properly addresses the real clinical question. When there is a potential benefit from a substance 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. [74]. Based on my physiological analysis of Cl^-, renal tubular function may be more important than glomerular filtration, although they are likely related. Diabetics and patients who have recently received intravenous contrast might be at higher risk. Animal studies suggest that volume status and use of catecholamines modify responses to Cl^- [40]. Patients who are expected to receive large amounts of fluid are likely at higher risk because of the larger total load of Cl^-, and for surgical cases this can be predicted by the type of surgery, whether it is done as an emergency, the risk of hypotension, and the expected length of surgery as was done by McCluskey et al. [74].

The study by Shaw et al. [72] showed that there were more tests performed in subjects given solutions with higher Cl^-. This likely reflects clinicians reacting to the acidemia produced by hyperchloremia and not appreciating the cause. Better recognition of an inevitable rise in Cl^- with large infusion of saline solutions and the consequent decrease in base excess, pH, and HCO_3^- could eliminate this problem, for outside of reducing Cl^- intake nothing further likely needs to be done.

Conclusion

An elevated Cl^- concentration in the body is an unphysiological condition. The potential significance is elevation of hydrogen ion concentration and consequent effects on functions of multiple proteins. The evidence to date suggests that moderate amounts can be handled by the body, but the effect of larger amounts of Cl^--rich solutions in higher risk subjects is not known. It needs to be determined whether it is the concentration of Cl^- that counts or the total body excess amount of Cl^-. 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 when this is not recognized, as well as unnecessary clinical interventions. 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, which are not pragmatic but include a protocol that regulates total volume given as well as the type of fluid given. It also must address specific endpoints of processes that can be affected by increased Cl-, which include bowel and kidney function but also immunity, coagulopathy, red cell survival, and response to catecholamines.

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Chapter 12
Positive Fluid Balance and Patients' Outcomes

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.

Keywords Fluid balance • Edema • Venous congestion • Heart failure • Sodium restriction • Colloid • Crystalloid • Fluid administration • Sodium retention

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 posthospitalization mortality.
3. Given that many patients do not spontaneously diurese administered fluid, judicious use of intravenous fluid and close monitoring of fluid balance are critical.

J. Danziger, MD, MPhil
Division of Nephrology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
e-mail: jdanzige@bidmc.harvard.edu

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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. 12.1). The cell membrane separates the intracellular space,

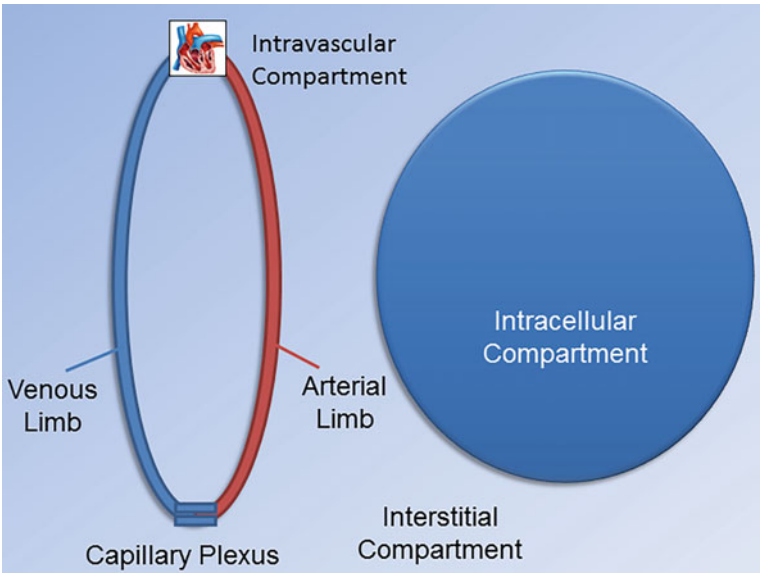

Fig. 12.1 Although the distribution of body fluid has traditionally been divided into three compartments, namely, the intravascular, interstitial, and intracellular compartments, this somewhat oversimplified approach fails to reflect the complex physiology of fluid hemodynamics. First, the capillary 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 glycalyx 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. 12.1, 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. 12.2, 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 decreased renal perfusion and consequent decreased renal

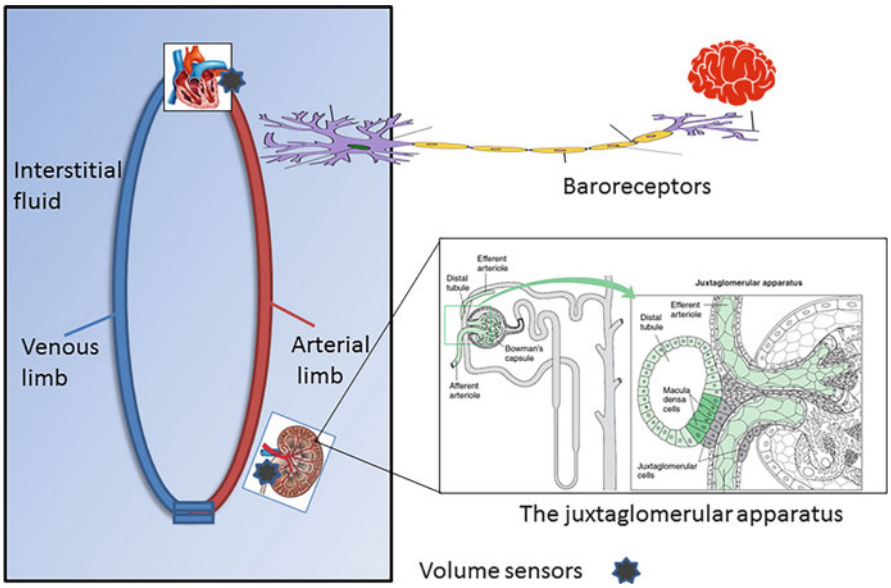

Fig. 12.2 Although the extracellular compartment is made up of the interstitial and intravascular compartments, this separation is somewhat arbitrary, since the capillary wall is highly permeable to sodium and water, and fluid continuously moves between the two compartments. No accurate mechanisms to 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

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.

Table 12.1 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]

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 12.1) 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 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 2,600 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 3,687 ml (range 1,300–8,711) 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 to 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 to 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. 12.3. 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.

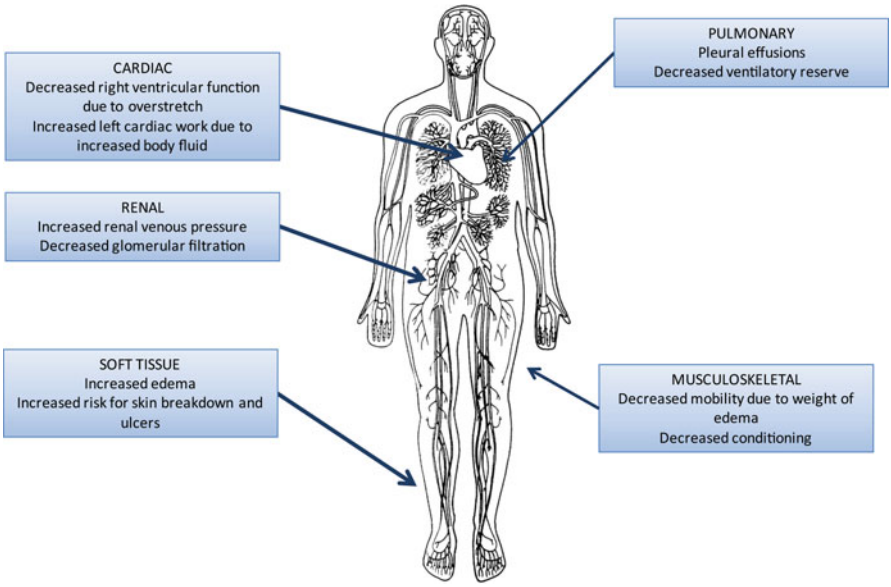

Fig. 12.3 Potential effects of positive fluid balance. Increased extracellular fluid will ultimately distribute into the vascular and interstitial spaces, with potential negative sequelae across multiple organ systems. Venous congestion likely impairs right ventricular function by overstretching the 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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Chapter 13
Fluid Management and Its Role in Enhanced Recovery

Andrew F. Cumpstey, Michael P.W. Grocott, and Michael (Monty) G. Mythen

Abstract Enhanced recovery programs have repeatedly been shown to safely reduce perioperative morbidity and hospital length of stay for surgical patients, and they are being used 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 and maintain a "zero-balanced" approach, patients should start surgery minimally dehydrated, be given fluids only 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. 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.

A.F. Cumpstey, MA(Cantab), BMBCh, MRCP (✉) • M.P.W. Grocott, BSc, MBBS, MD, FRCA, FRCP, FFICM
Department of Anesthesia and Critical Care Medicine, University of Southampton, Southampton, UK
e-mail: a.cumpstey@soton.ac.uk

M.G. Mythen, MBBS, MD, FRCA, FFICM, FCAI(Hon)
Department of Critical Care, Anaesthesia and Perioperative Medicine, University College London, London, UK

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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. A "zero-balance" fluid approach 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 1,676 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 13.1 [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 management should be an essential component of any enhanced recovery protocol. The challenge is in defining what constitutes "optimal."

Table 13.1 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.

Fluid Therapy in Enhanced Recovery: A "Zero-Balance" 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. 13.1 [24].

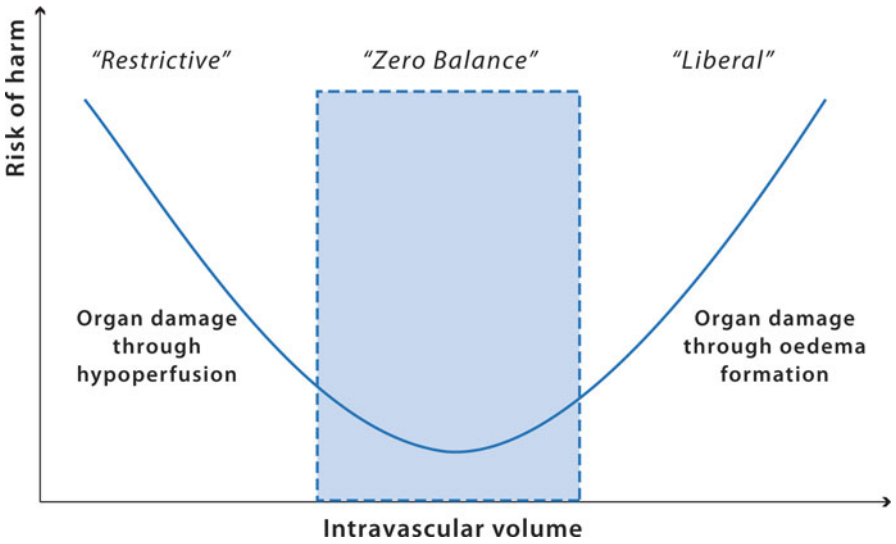

Fig. 13.1 Both "restrictive" and "liberal" fluid administration increase the risk of end-organ damage compared to a "zero-balance" approach through hypoperfusion or tissue edema generation, respectively (Adapted from [24])

Unfortunately, terminology in this area has often been confusing historically. "Liberal fluid therapy" was initially encouraged perioperatively to maintain a proposed "3rd 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." This avoids these misinterpretations and encourages an approach that simply replaces what is lost (e.g., insensible loss through ventilation and respiration, or volume loss from intraoperative hemorrhage) [21, 24].

"Zero-balance" is also the term that the American Society for Enhanced Recovery (ASER) has adopted in their guidelines on perioperative fluid management to encourage this approach [26]. Again, the ASER guidelines emphasize the importance of maintaining a zero-balance approach throughout the preoperative, intraoperative, and postoperative phases of surgery, but as different considerations arise at each of these different points, it might be helpful to consider how this approach should apply to each of these stages 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 maintain a zero-balance approach 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 [27, 28]. The European Society of Anaesthesiology also now encourages both adults and children to drink fluids up to 2 h preoperatively in its guidelines [29].

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 [30–32]. 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 [33, 34]. 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. These drinks also decrease patient discomfort while waiting for surgery as well as decreasing postoperative insulin resistance through increasing insulin activity [35, 36]. They can safely be taken 2–3 h prior to surgery depending on the nutritional content [37].

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].

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 excess of this rate can rapidly lead to harm and postoperative complications (such as ileus as explained earlier) [23, 38]. While acknowledging that more liberal fluid administrations of up to 20 or 30 ml/kg/h might confer some benefits in ambulatory patients (such as decreasing postoperative drowsiness, nausea, and pain), international guidelines recommend that maintenance fluids should be given at 1–2 ml/kg/h for all longer or more major operations [16, 39].

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 [39]. 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" [39].

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, 40, 41].

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 [42]. 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 [41]. 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 [39].

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 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 [43].

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 a "zero-balance approach" 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 [44].

In other words, an *individualized* zero-balance 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 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 (as per 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 [45, 46].

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 [47].

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 [48].

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 10 years ago. 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 [49].

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 [50, 51].

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 [51]. 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.

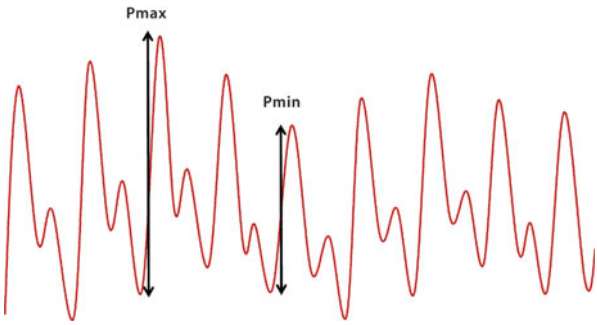

Fig. 13.2 Pulse pressure variation is the percentage difference between the maximum pulse pressure (P_{max}) and the minimum pulse pressure (P_{min})

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 [39, 42, 50]. 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 [50].

Pulse pressure variation (see Fig. 13.2) 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 [42]. 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 [52]. 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 [42].

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 [53, 54].

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 [42, 50, 55].

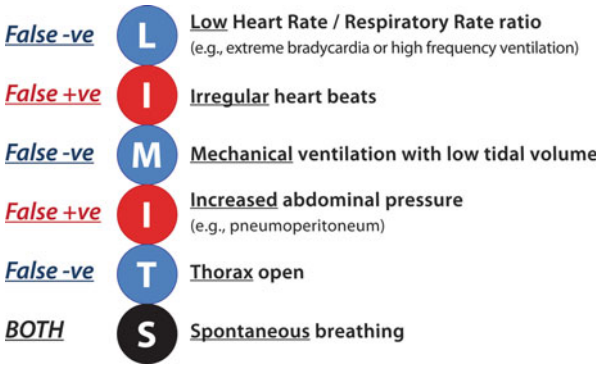

Fig. 13.3 The "LIMITS" to using pulse-pressure variation monitoring, and whether a false-positive or false-negative result should be expected in each case (Adapted from [56])

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, 42, 52]. 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 [56]. See Fig. 13.3 [56].

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, 41, 50].

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, 57].

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 [58, 59]. Soon after this, in 1978, Bland et al. proposed that oxygen delivery would be a useful therapeutic goal to target [60]. 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 [61].

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 [62].

Different ways of monitoring cardiac output include everything from using routine monitoring to visualize 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 [55, 63, 64].

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 [63].

In 2012, a Cochrane systematic review of 31 trials with a total of more than 5,000 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) [65].

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, 65].

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 [66].

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 1,500 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: 1,994 ml in the goal-directed fluid group compared to 1,614 ml on average in the restrictive group, and there was no clinically relevant difference in the hemodynamic variables [67].

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 (1,500 ml in the restrictive compared to 2,190 ml in the goal-directed group, $p=0.008$) [68].

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 [69].

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 3,638 ml in the goal-directed group and 3,834 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 emphasize the importance of a zero-balance fluid management approach in this improvement [21, 67, 70].

So, where does this leave goal-directed fluid therapy in enhanced recovery protocols? 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 [71]. 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 1,000 patients, and had this initial target been reached, then may be these two end points would have reached significance, but that remains unknown [71].

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 [71].

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

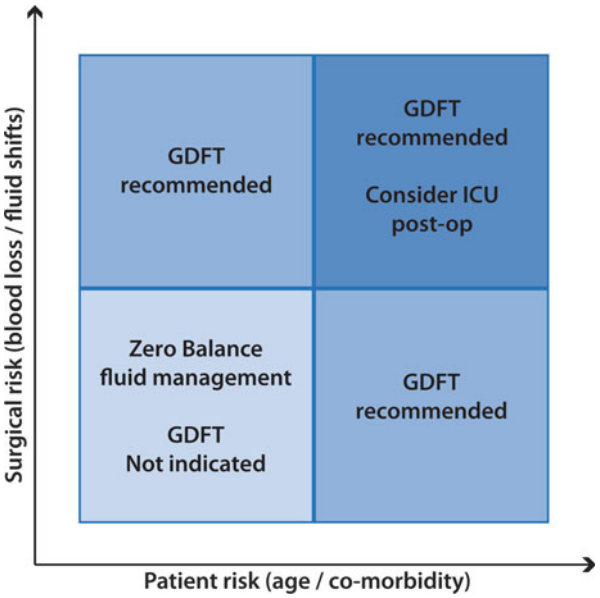

Fig. 13.4 The fluid management approach used should depend on both patient and surgical risk factors, with goal-directed fluid therapy (GDFT) indicated in higher risk cases (Adapted from [21])

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 [71].

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 post-operative 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, 69, 71, 72].

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 [57].

Currently, consensus UK guidelines recommend using an individualized fluid plan with a zero-balance approach 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. 13.4 [21]. 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 13.2 [22, 39, 73].

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

Table 13.2 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, 38, 72]

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, 39].

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.

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 be harmful [21]. 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 [73]:

- 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, 73]. 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 [74]. However, at least two other large randomized trials have recently suggested 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 [75, 76].

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 [77]. 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, and they are gradually being used in more and more surgical specialties [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 a zero-balance approach throughout the perioperative period [21]. 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, 42]. 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 [39]. 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 [78].

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Part II
Case Scenarios Management During Colorectal, Orthopedic, and Spine Cases

Chapter 14
Case Scenario for Perioperative Fluid Management in Major Orthopedic Surgery

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

Keywords Orthopedic surgery • Anesthesia • Intraoperative • Fluid Management • Transesophageal echocardiography • Goal-directed therapy

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

W. Ali Sakr Esa, MD, PhD
Section Head Orthopedic Anesthesia, Department of General Anesthesia and Pain Management, Cleveland Clinic Lerner College of Medicine, Cleveland Clinic, Cleveland, OH, USA
e-mail: alisakw@ccf.org

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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 3,000 ml normal saline, 5,000 ml lactated Ringer's, 1,500 ml 5 % albumin, 2,900 PRBCs, four units fresh frozen plasma (FFP), and two sets of platelets for a 10-hour surgery. The estimated blood loss was 4,000 ml. Urine output was 1,800 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 14.1 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].

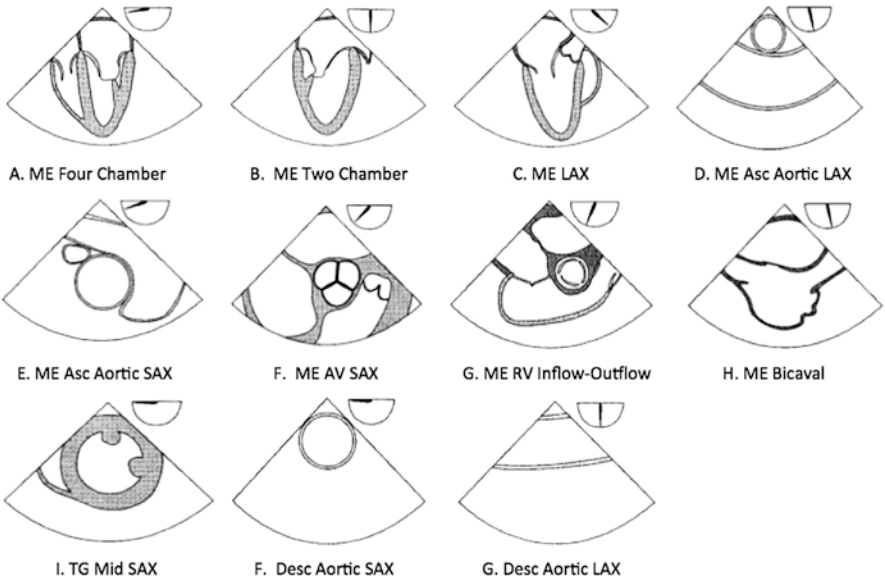

Fig. 14.1 List of the 11 views suggested by the American Society of Echocardiography and Society of Cardiovascular Anesthesiologists guidelines on basic perioperative transesophageal echocardiography. *ME* midesophageal, *LAX* long-axis view (Reprinted with permission from Reeves et al. [13])

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 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:

$$SV = VTI \times CSA_{LVOT}$$

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:

$$CSA_{LVOT} = 0.785 \times \text{diameter}^2$$

The CSA of the LVOT is usually obtained from the midesophageal long axis (ME LAX) view at 110–140° (Fig. 14.2) [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. 14.3) [12, 16, 17].

Much controversy exists about the role of crystalloids and colloids in fluid therapy. 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

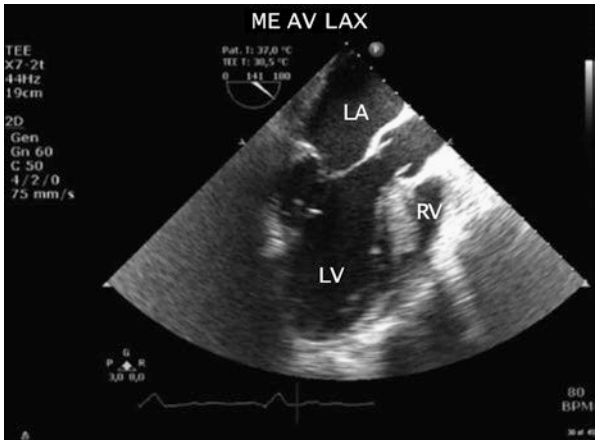

Fig. 14.2 Transoesophageal echocardiography view (midesophageal long-axis view) used to measure left ventricular outflow tract diameter usually best imaged at a multiplane angle of 110–140°. *AV* aortic valve, *LA* left atrium, *LV* left ventricle, *RV* right ventricle, *ME AV LAX* midesophageal aortic valve long-axis view (Modified with permission from Møller-Sørensen et al. [16])

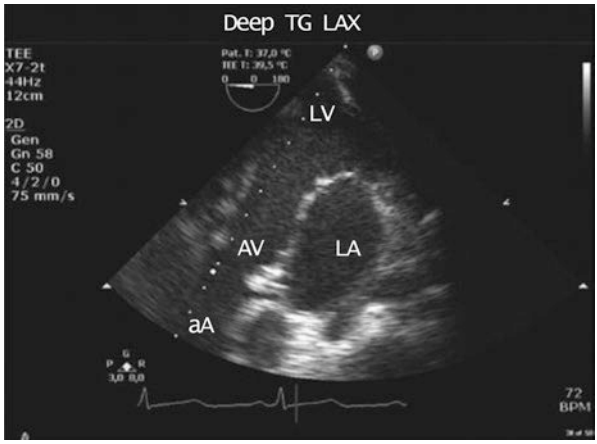

Fig. 14.3 Transoesophageal echocardiography view (deep transgastric long-axis view), used to measure velocity–time integral. *AV* aortic valve, *LA* left atrium, *LV* left ventricle, *aA* ascending aorta, *TG LAX* transgastric long-axis view (Modified with permission from Møller-Sørensen et al. [16])

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 [18].

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.

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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Chapter 15
Case Scenario for Perioperative Fluid Management for Major Colorectal Surgery

Kamal Maheshwari

Abstract Fluid management should be guided by dynamic hemodynamic parameters, patient factors, and surgical factors. The conventional approach to some set rule and formulas is being challenged and being replaced by a goal-directed approach. 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.

Keywords Colorectal surgery • Anesthesia • Intraoperative • Fluid management • Postoperative ileus • Enhanced recovery after surgery • Goal-directed therapy

Introduction

Fluid management should be guided by dynamic hemodynamic parameters, patient factors, and surgical factors. The conventional approach to some set rule and formulas is being challenged and being replaced by a goal-directed approach. 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 [1].

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. The role of goal-directed therapy

K. Maheshwari, MD, MPH
Acute Pain Management, Outcomes Research, Anesthesiology Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: MAHESHK@ccf.org

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(GDT) using dynamic hemodynamic monitors is evolving, but the data do suggest that a restrictive fluid regimen results in improved patient outcomes. 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. 15.1) [4, 5]. In 2012, Gustafsson et al. published ERAS Society recommendations for perioperative care in elective colonic surgery [6]. 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 15.1) [7].

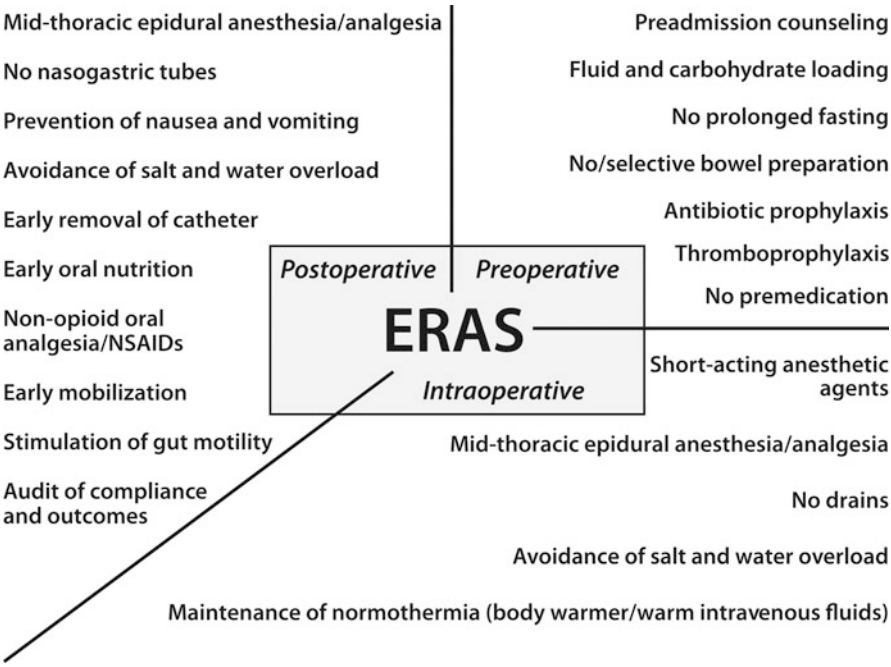

Fig. 15.1 Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery: pathophysiological considerations (Modified with permission from Varadhan et al. [63])

Table 15.1 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. [7]
NSAIDs, nonsteroidal anti-inflammatory drugs; *ERPs*, enhanced recovery programs;
++, definite benefit; +, possible benefit; ±, no benefit; –, possible harm

Fluid Management

Postoperative complications are common [8, 9], and reducing complications thus decreases both cost and mortality [10]. 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 [11]. *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 [12, 13]. *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.

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) [14]. 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 [15, 16]. GDT has also been shown to be cost-effective and results in better clinical outcomes in high-risk surgical patients [17]. GDT reduces mortality most in patients undergoing high-risk surgery (>20 % mortality), although complication rates are reduced in all surgical groups [8].

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) [18], LiDCO (LiDCO Ltd, London, UK) [19], NICOM (Cheetah Medical, Tel Aviv, Israel) [14, 18], Flotrac (Edwards Lifesciences, Irvine, CA, USA) [20, 21], and NexFin (BMEYE, Amsterdam, The Netherlands) [22, 23], 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 [24]. 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 [25]. 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 [26, 27]. NexFin accurately estimates blood pressure [28] and cardiac output in healthy adults [26, 29], but whether using the system reduces complications remains unknown [30].

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 [18]. 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 [31]. The Flotrac software has been updated multiple times (now Flotrac 3) and has been validated in septic patients with low systemic vascular resistance (SVR) [32]. 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) [33]. Other LiDCO-based studies are in progress [34].

Evidence for GDT

Numerous studies demonstrate that GDT reduces complications, infections, and the duration of hospitalization [35]. Results are generally similar, even though devices and protocols differ [36–38]. For example, Benes et al. used colloid and dobutamine infusion to optimize cardiac index and stroke volume variation in a high-risk

Table 15.2 Evidence for perioperative goal-directed therapy

	Study design	Equipment	Parameter	Fluid	Outcomes
Donati [49]	RCT	CVP and oxygen extraction	DO_2	Colloid	60 % decrease in postoperative complications 16 % decrease in LOS
Benes [36]	RCT	Vigileo/FloTrac system	SVV	Colloid	56 % reduction in 30-day postoperative complications 10 % reduction in LOS
Cecconi [37]	RCT	Vigileo/FloTrac system	SV	Colloid	20 % reduction in postoperative complications
Kuper (NHS) [39]	Before/after comparison	Esophageal Doppler	SV	Crystalloid/ colloid	25 % decrease in LOS (3.7 days decrease)
Wang [50]	RCT	Vigileo/FloTrac system	SVV	Crystalloid/ colloid	19 % decrease in LOS
Ramsingh [51]	RCT	Vigileo/FloTrac system	SVV	Colloid	33 % decrease in LOS (2.5 days decrease)
Pearse et al. (2014) [16]	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.

elective abdominal surgery group and reported a 56 % reduction in 30-day postoperative complications along with a 10 % reduction in hospital LOS [36]. 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 [39]. Esophageal Doppler has been successfully used to measure cardiac output and stroke volume [40–47]. 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 [17].

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 [16]. Early GDT also failed to improve outcomes in patients with early septic shock [48]. Nonetheless, most studies do report benefit from GDT, and the major ones are summarized in Table 15.2 [16, 36, 37, 39, 49–51].

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″);| 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 [52, 53].

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. 15.2). 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 1,750 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.

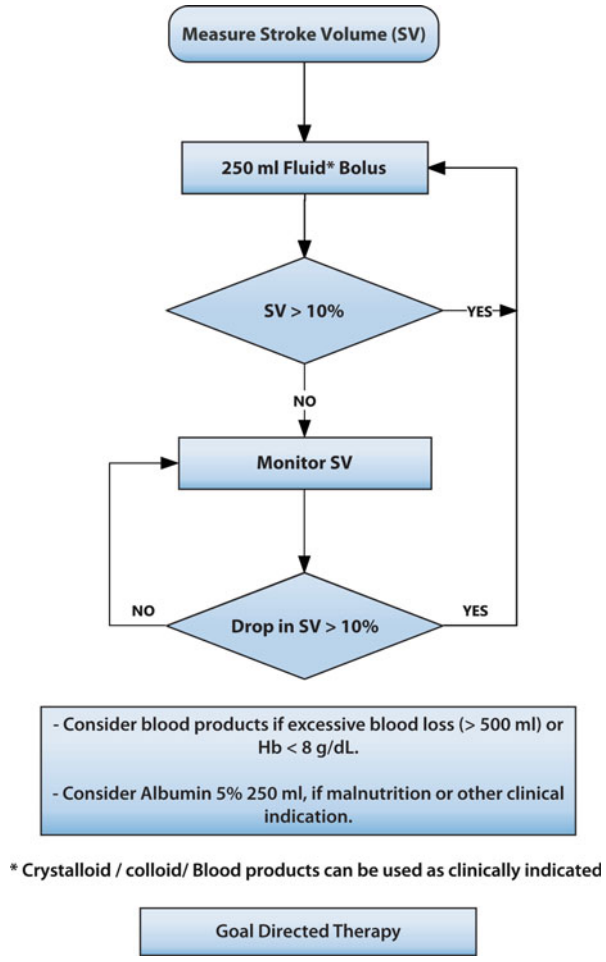

Fig. 15.2 Goal-directed fluid therapy algorithm

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.

Discussion

Individuals differ in their response to surgical stress. The age, functional status, and comorbidities make them prone to postoperative complications and mortality [9, 54, 55]. 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 [56, 57].

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 [58]. 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 [59].

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" [4].

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 [60]. 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 [61, 62]. 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 [14]. 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 [15, 16]. GDT has also been shown to be cost-effective and result in better clinical outcomes in high-risk surgical patients [17]. GDT reduces mortality mostly in patients undergoing high-risk surgery (>20 % mortality), although complication rates are reduced in all surgical groups [8].

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 [11]. 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. Fluid management should be guided by dynamic hemodynamic parameters, patient factors, and surgical factors. 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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Chapter 16
Case Scenario for Fluid Therapy in Septic Shock

William Phillips

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, the 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. Concurrent with source control and early antibiotic administration, early and aggressive fluid therapy, maintenance of tissue perfusion, and judicious application of inotropic support remain a cornerstone of septic shock therapy. Early goal-directed therapy (EGDT) has been widely adopted as a protocolized methodology to ensure early and aggressive fluid resuscitation (in addition to vasopressors, steroids, and timed antibiotic administration). It has been postulated that bundle implementation may improve survival. Perioperative goal-directed fluid management may also affect outcome.

Keywords Hypovolemia • Septic shock • Fluid therapy • Crystalloid • Colloid • Goal-directed fluid management

Key Points

1. Determining fluid responsiveness is a dynamic process that requires a valid and continuous assessment of cardiac performance.
2. Lactated Ringer's may be the optimum resuscitation fluid.
3. Albumin use may have a particular niche for resuscitation utilization in severe septic shock.
4. Early but very judicious vasopressor deployment may help obviate excessive administration of intravenous fluids.
5. Positive fluid balance has a linear adverse effect on survival in the intensive care unit (ICU).

W. Phillips, MD
Department of Anesthesiology, Center for Critical Care Medicine, Cleveland Clinic, Cleveland, OH, USA
e-mail: PHILLIW@ccf.org

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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/hypotension, 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/upper arm 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; heart rate, 134; SaO_2, 92 % (FiO_2, 60 %); respiratory rate, 16 on ventilator; temperature, 35.7 °C; central venous pressure (CVP), 9 mmHg.

Chest radiograph: patchy bilateral infiltrates

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; 90 % PMNs hemoglobin 11 mg/dl, hematocrit 34 %, platelet count 124,000
- Electrocardiogram (EKG)—sinus tachycardia with nonspecific ST and T wave changes.

Upon arrival to the ICU, his intravenous fluids are changed to lactated Ringer's (LR), and he received boluses totaling 40 ml/kg and is started on an infusion of 200 ml/h. His norepinephrine is increased to 0.1 mcg/kg/min, and vasopressin is added as an infusion of 0.02 units/h (understanding that it does not improve mortality but may decrease the infusion rate of norepinephrine) [1]. Noninvasive cardiac output monitoring with pulse pressure variation (PPV) analysis is initiated, and a baseline ultrasonographic inferior vena cava (IVC) assessment is performed indicating a near collapsed IVC, despite a concurrent CVP of 10 mmHg. Periodic IVC assessment is repeated concurrently with measurements of serum lactate, and vasopressors are titrated with bolus fluid administration to achieve a 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 12.5 g each, and each infused over a period of 2 h. Albumin is chosen to

potentially decrease the peak positive fluid balance in deference to the effect of that parameter on ultimate outcome. Two units of packed red blood cells (PRBCs) are also administered for a fall in his hemoglobin to 7.5 g/dl with a concurrent serum lactate level of 5.2 mEq/l. Red cells are utilized at this juncture (at a higher "transfusion trigger" than might normally be chosen) due to his lactic acidosis, ongoing vasopressor requirements, and to potentially offset/avoid worsening his very large positive fluid balance due to crystalloid infusions.

The patient required two subsequent trips to the operating room for debridement, but at the 72 h mark had stabilized markedly with discontinuation of his vasopressors, and a fall in his creatinine to 1.4 mg/dl. Judicious diuresis was initiated guided by ongoing continuous assessment of cardiac index (CI)/PPV, and periodic ultrasonographic assessment of his IVC diameter.

He was able to be extubated on ICU day number 6 with, at that time, an overall positive fluid balance of 9 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 [2]. 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.

Concurrent with source control and early antibiotic administration, early and aggressive fluid therapy, maintenance of tissue perfusion, and judicious application of inotropic support remain a cornerstone of septic shock therapy [3, 4]. Early goal-directed therapy (EGDT) has been widely adopted as a protocolized methodology to ensure early and aggressive fluid resuscitation (in addition to vasopressors, steroids, and timed antibiotic administration) [5–7]. It has been postulated that bundle implementation may improve survival [8, 9]. Perioperative goal-directed fluid management may also affect outcome [10].

Fluid resuscitation strategies are based on the premise that regardless of fluid type, as with antibiotic administration, early resuscitation decreases mortality due to abrupting the duration of hypotension [11]. Despite the accepted 6-h window for lactate normalization, aggressive fluid resuscitation may benefit even if delayed as much as 24 h [12, 13]. Critical to successful fluid resuscitation is the ability to assess volume responsiveness (VR—an increase in cardiac index or performance with fluid administration) in a linear and continuous fashion [14].

Whether there is true benefit from a protocolized (versus individualized) approach to fluid resuscitation is arguable. 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 clear patient 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 [15–18].

Another 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) as preload parameters are poor predictors of fluid responsiveness, not only in septic patients but also in the perioperative setting [19–21].

Although CVP monitoring may have some utility in the initial stages of sepsis resuscitation, it loses value after 12 h [4]. Ultrasonographically determined inferior vena cava (IVC) size (absolute) may also be a poor predictor of volume responsiveness (VR) [22]. Respiratory variation of the IVC as a barometer for VR has been more widely adopted in the emergency medicine setting, but validity of this methodology is not fully established [23, 24]. Measurement of right internal jugular distensibility has also been nominated as a potential surrogate marker for IVC assessment [25]. There is the additional issue of serial ultrasonographic examinations failing to provide a continuous or "dynamic" patient parameter. Central venous oxygen saturation ($ScVO_2$) is also a questionable titratable parameter in septic patients, as it may be clinically elevated due to peripheral shunting [26]. Higher $ScVO_2$s may even be associated with a higher mortality [27]. Having a reliable marker for adequate volume resuscitation is particularly critical in septic shock patients as over-resuscitation 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 [28].

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 [29, 30]. 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 [31]. 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].

A conservative (perhaps a better word is "appropriate") fluid management strategy reduces mortality in septic shock [32, 33]. This trend has also been demonstrated with elective surgery [34, 35] and after high-risk surgery by means of rigorous titration of fluid loading to optimization of pulse pressure variation (PPV) or stroke volume as determined by transesophageal Doppler [10, 36]. 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) [29]. 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 [37].

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 [29]. The endothelial glycocalyx, a 1-mm thick membrane-bound matrix of glycoproteins and proteoglycans, is compromised in inflammatory states and by hypervolemia [38]. 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 [39].

These data underscore the need to highly individualize fluid management and to couple tightly fluid management 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 [40, 41].

Arterial pulse containing variation analysis (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 [14]. 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 nonresponsiveness [19]. 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 [20, 42]. Small tidal volume mechanical ventilation, spontaneously breathing patients, cardiac arrhythmias, and cases of right or left ventricular failure may yield less reliable results [43, 44].

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 include FloTrac (Edwards Lifesciences, Irvine, CA. USA), LiDCO (LiDCO, London, United Kingdom), PiCCO (Pulsion Medical Systems, Feldkirchen, Germany), and MostCare (Vytech, Padova, Italy). These systems require varying degrees of recalibration but may have utility in trending calculated CO/CI [19]. Esophageal Doppler measurement of aortic diameter, blood flow velocity, and calculated cardiac output is another alternative methodology [45]. Transthoracic Doppler assessment of the aortic velocity time integral (VTI) by the USCom systems (Uscom, Sydney, Australia) may also be utilized with the limitations of requiring an accurate Doppler signal and the lack of continuous data [46]. Transcutaneous transthoracic pulsatile flow assessment due to blood phase shifts calculated from bioreactance data is available through the NICOM system (Cheetah Medical, Tel Aviv, Israel) and is potentially a more accurate modality than older bioimpedance-based systems [47]. 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 [48, 49].

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 [50]. There has also been the suggestion that albumin may possess antioxidant potential [51]. Albumin may also help stabilize the endothelial glycocalyx [52]. The Saline Versus Albumin Fluid Evaluation (SAFE) trial evaluated albumin versus crystalloid for hypotensive resuscitation with no clear advantages to albumin, but subsequent subgroup analysis for patients with severe sepsis suggested an albumin benefit [53, 54]. These data conflict with other evaluations of albumin use in septic shock, where no mortality advantage and increased costs/length of stay have been suggested [55, 56]. 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 [57, 58]. 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 [59, 60]. 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 [61]. 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 [59, 62].

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 [63]. 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 [64]. 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 [65, 66].

Overall, 0.9% sodium chloride (normal saline [NS]) is the most widely used resuscitation fluid [67]. Concern however has arisen that the high chloride content of NS contributes to both acute kidney injury and increased mortality in critically ill patients [68, 69]. The chloride effect on the kidney may be due to afferent renal arterial vasoconstriction [70]. 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 SPLIT (0.9% Saline vs Plasma-Lyte 148 for ICU fluid therapy) trial prospectively compared NS to buffered fluids in more than 2,000 ICU patients with diverse medical and surgical diagnoses (4% of patients were septic) and found no difference in mortality or evidence of renal injury [71].

In a retrospective cohort of specifically septic patients, no increase in mortality or renal injury was noted with saline [55]. However, in a perioperative trial involving patients undergoing major vascular surgery, NS was associated with a higher risk of dialysis compared to Plasma-Lyte [72]. NS is also well associated with hyperchloremic nonanion gap metabolic acidosis [73] and may also predispose to a higher incidence of coagulopathy [74].

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 [75]. As a base, lactate serves as an ultimate source of bicarbonate with a resultant elevation in plasma pH. The use of LR is also not contraindicated in liver disease [76]. Based on these data and the unclear linkage between chloride and acute kidney injury, LR as a prototypical buffered solution may offer real advantages over NS.

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Chapter 17
Case Scenario for Fluid Management in Liver Resection

Maged Argalious and Harendra Arora

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.

Keywords Liver resection • Hypercoagulable state • Thromboelastography • Coagulation • Transfusion • Cell salvage • Pulse pressure variation (PPV) • Fluid responsiveness • Portal triad clamping • Total vascular exclusion (TVE)

M. Argalious, MD, MSc, MBA, MEd (✉)
Anesthesiology Institute, Cleveland Clinic, Cleveland Clinic Lerner College of Medicine, Center for Anesthesiology Education, Cleveland, OH, USA
e-mail: ARGALIM@ccf.org

H. Arora, MD
Department of Anesthesiology, University of North Carolina Hospitals, Chapel Hill, NC, USA

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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. 17.1).

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.

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

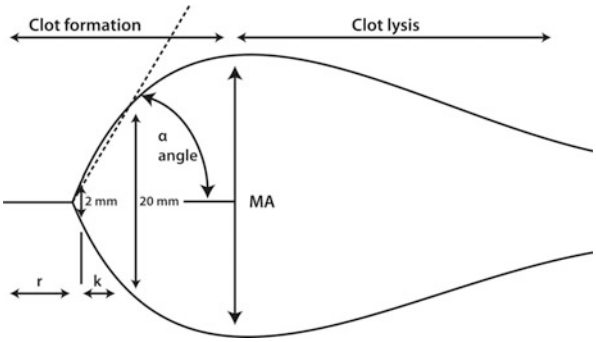

Fig. 17.1 A normal thromboelastographic tracing. (1) *r* – time is the time elapsed from placement of the sample in the cuvette until the tracing amplitude reaches 2 mm; it denotes the rate of initial fibrin formation and is functionally related to plasma clotting factors. (2) *k* is measured from r 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

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 17.1 shows the correlation of thromboelastography (TEG) with phases of hemostasis and standard coagulation tests [7].

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

Table 17.1 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

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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Chapter 18
Case Scenario for Fluid Management During Major Spine Surgery

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.

Keywords Intraoperative hypovolemia • Anemia • Blood conservation modalities • Preoperative risk assessment for spine surgery • Lumbar spine surgery • Acute blood loss

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.

V.L. Baughman, MD
Department of Anesthesiology, University of Illinois, Chicago, IL, USA
e-mail: VBaughma@uic.edu

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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 18.1).

Table 18.1 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 reoperative thoraco-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 18.2).

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 cardio-

Table 18.2 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 1,000 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

myopathy 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 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

Table 18.3 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

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.

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 18.3)

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 oximetry photoplethysmography
- 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 3,000 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 1,167 ± 998 ml with a range from 32 to 3,745 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 normovolemic hemodilution, 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 normovolemic hemodilution 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]. Isovolemic hemodilution 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 4,000 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 18.4).

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 1,500 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 18.5).

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

Table 18.4 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), 1,500 ml albumin, 2 units platelets

Table 18.5 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), 1,500 cc albumin, 2 unit platelets; Hgb/Hct – hemoglobin/hematocrit

back pain, radiculopathy, neurogenic claudication, and facet/ligament hypertrophy. Disc herniation may be present. Flexion, by sitting or leaning forward, increases spinal canal size by stretching the protruding ligamentum flavum, 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 con-

tinuous 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 5,887 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 intraopertive hypovolemia 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, preop-

erative 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 18.6).

Table 18.6 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

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 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 18.1 and 18.2 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 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.

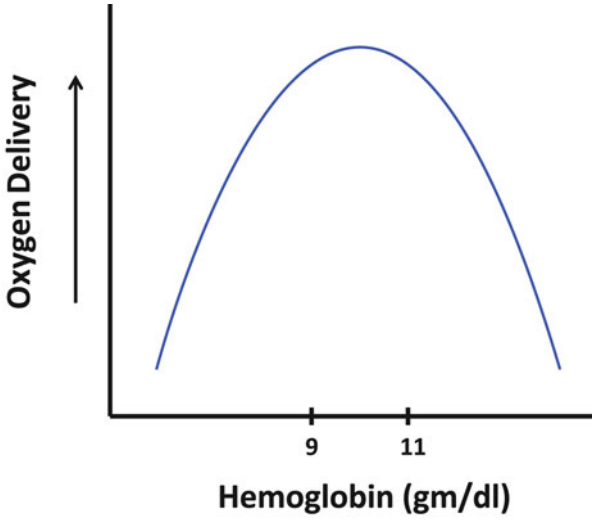

Fig. 18.1 Hemoglobin, oxygen delivery, and anemia

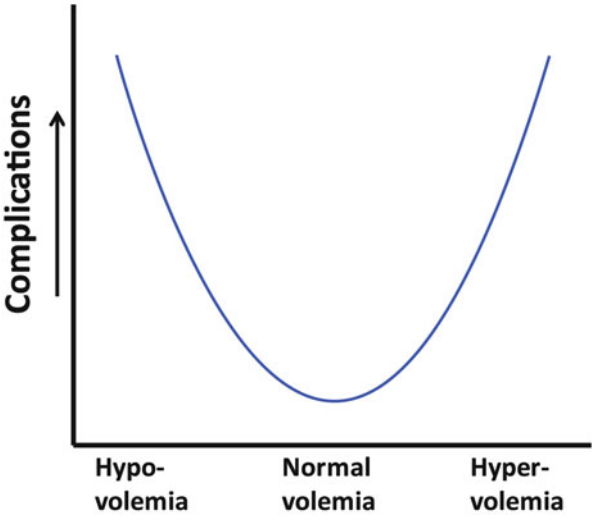

Fig. 18.2 Intravascular volume and complications

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Chapter 19
Case Scenario for Fluid Management After Subarachnoid Hemorrhage in the Neuro-intensive Care Unit

Jamil R. Dibu and Edward M. Manno

Abstract Subarachnoid hemorrhage is a cerebrovascular emergency that has potential for a prolonged and complicated hospital course, carrying high rates of morbidity and mortality. The most common cause of spontaneous subarachnoid hemorrhage is aneurysm rupture. Most patients with aneurysmal subarachnoid hemorrhage will need to be monitored closely in an intensive care unit after treatment of the ruptured aneurysm to monitor and prevent potential neurological and medical complications. Neurological complications include seizures, hydrocephalus, high intracranial pressure, cerebral vasospasm, and delayed cerebral ischemia, all of which can worsen outcome of postsubarachnoid hemorrhage. Medical complications that can occur in these patients include hyponatremia, which is commonly caused by either cerebral salt wasting syndrome or syndrome of inappropriate antidiuretic hormone secretion. Close monitoring of the extracellular fluid status and accurately diagnosing the etiology of hyponatremia is important in order to provide the appropriate management and avoid its potential sequelae such as hypovolemia, cerebral edema, and secondary symptomatic cerebral vasospasm.

Keywords Subarachnoid hemorrhage • Cerebral vasospasm • Delayed cerebral ischemia • Hyponatremia • Hypovolemia • Cerebral salt wasting • Syndrome of inappropriate antidiuretic hormone secretion

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 vasospasm and delayed ischemic infarction.

J.R. Dibu, MD (✉) • E.M. Manno, MD
Department of Neurocritical Care, Cerebrovascular Center, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: dibuj@ccf.org

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3. Fluid administration and inducing hypertension are the mainstays of treatment of aneurysmal subarachnoid hemorrhage (aSAH) patients who develop cerebral vasospasm. Triple H therapy is not recommended.
4. Recognizing high-grade aSAH patients who develop neurogenic stunned myocardium is important, as adding inotropes and using goal-directed fluid therapy (GDFT) can assist in achieving appropriate cerebral blood flow (CBF) to treat vasospasm.
5. Hyponatremia in aSAH patients carries additional risk for morbidity and mortality. The two common etiologies are syndrome of inappropriate antidiuretic hormone (SIADH) and cerebral salt wasting (CSW). Avoiding and correcting hypovolemia and hyponatremia with hypertonic solutions is key to preventing worse outcomes.

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a neurological emergency with significant morbidity and mortality. This devastating cerebrovascular event has a reported mortality up to 67 %, of which half will die within 2 weeks of the ictus, and 20 % of hemorrhagic stroke survivors will be left with significant functional and cognitive disability [1]. The initial hemorrhage has direct and secondary neurological effects in the early and late course of the illness such as rebleeding, seizures, hydrocephalus, and delayed cerebral ischemia (DCI) related to vasospasm. Medical complications are not uncommon in aSAH patients with multisystem involvement of the heart, lungs, and kidneys, alongside possible infectious and endocrinologic complications. The severity of the presenting clinical grade of an aSAH patient and the potential risk of neurological and medical sequelae that follows the initial hemorrhage necessitates the need for close monitoring of aSAH patients in an intensive care unit (ICU) to prevent life-threatening complications [2].

Case Scenario

A 61-year-old man with a past medical history of hypertension and smoking presented to the emergency department (ED) with sudden onset bifrontal headache associated with nausea, vomiting, neck stiffness, and confusion. In the ED, his mental status deteriorated from being sleepy to being responsive to only deep sternal rub. He was intubated for airway protection. Computed tomography (CT) scan of the brain without contrast revealed diffuse thick subarachnoid hemorrhage with intraventricular extension and evidence of early hydrocephalus, as shown in Fig. 19.1. His initial blood pressure (BP) was 195/112. On laboratory workup he had normal metabolic panel, coagulation parameters, and platelets count. According to the wife, he had no recent head trauma and was not taking any blood thinners. CT angiography (CTA) of the head revealed an anterior

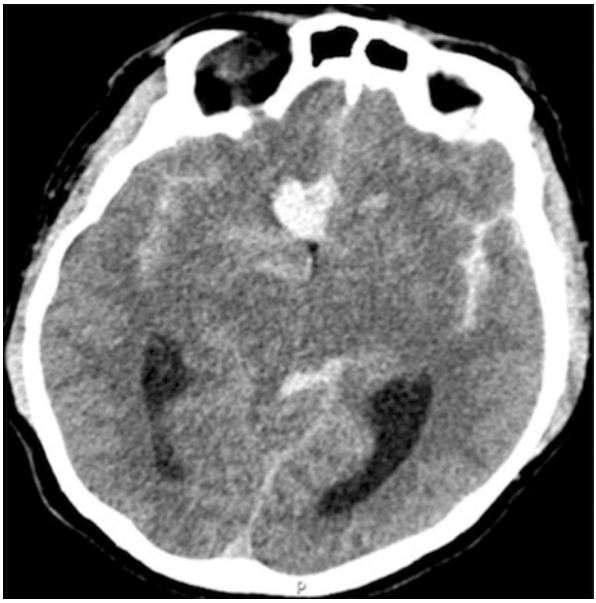

Fig. 19.1 Computed tomography brain scan without contrast showing diffuse thick SAH with IVH and early hydrocephalus

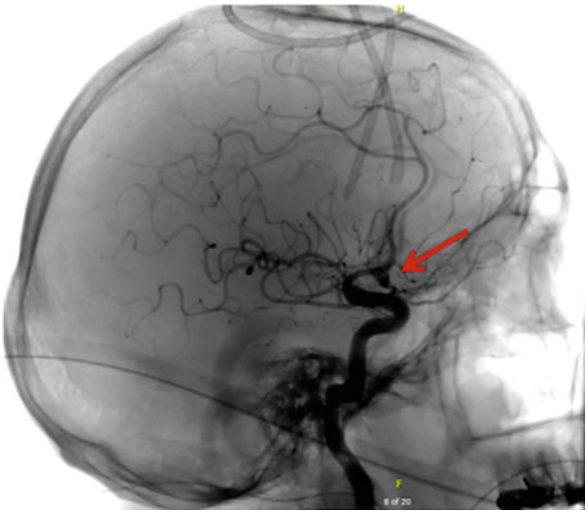

Fig. 19.2 Cerebral angiogram showing right 5.9 mm × 3.7 mm × 4.1 mm aneurysm. Anterior communicating artery (Acomm) aneurysm (*red arrow*)

communicating artery (Acomm) aneurysm. The neurosurgical team placed an external ventricular drain (EVD) and he was subsequently taken to the endovascular suite where he underwent successful endovascular coiling of the aneurysm. He was then transferred to the neurological intensive care unit (NeuroICU) for further management (Fig. 19.2).

Upon admission to the NeuroICU, the patient's BP was 174/90. The neurologic assessment of sedation revealed equal and reactive pupillary responses to light, cornea, cough, and gag reflexes were present, and he withdrew his upper and lower extremities to painful nail bed stimuli.

Discussion

What are potential early complications of aSAH and what are the appropriate preventative measures in management of aSAH?

Grading the severity of the clinical presentation using the *Hunt and Hess scale* (Table 19.1) in patients with aSAH provides a good prognostic indicator for their outcome [3]. The *modified Fisher Scale* (mFS) is a radiological scale that attempts to predict the risk of DCI from the development of cerebral vasospasm. This is obtained by grading the thickness of the subarachnoid hemorrhage with the presence or absence of intraventricular extension on the noncontrasted head CT (Table 19.2) [4]. The risk of cerebral vasospasm and subsequent DCI and worse outcomes increases with higher mFS grades.

Seizures after aSAH are reported in up to 26% of patients [5]. Prophylactic short-term use of antiepileptic drugs for 72 h may be considered, as seizures have been shown to be independently associated with worse outcome [6]. High-grade aSAH patients with a poor neurological exam should be monitored with continuous electroencephalography (cEEG) monitoring to detect and treat nonconvulsive seizures or status epilepticus, which can worsen outcomes [7].

The presence of intraventricular hemorrhage (IVH) in patients with subarachnoid hemorrhage puts patients at risk of developing acute obstructive hydrocephalus, which has been shown to be an independent risk factor for worse outcomes [8, 9]. Placement of an EVD is critical and lifesaving in this setting, serving as intracranial pressure (ICP) monitoring as well as allowing therapeutic drainage of cerebrospinal fluid (CSF) in cases of ventriculomegaly and high ICP.

Table 19.1 Hunt and Hess grading scale

Grade	Neurological assessment
I	Asymptomatic or mild headache and slight nuchal rigidity
II	No neurological deficit except cranial nerve palsy, moderate to severe headache, nuchal rigidity
III	Drowsiness or confusion or mild focal deficit
IV	Stupor, moderate to severe hemiparesis
V	Deep coma, decerebrate posturing, moribund appearance

Adapted from [3]

Table 19.2 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

Adapted from [4]
CT computed tomography

aSAH patients can present with various *cardiac* complications ranging from nonspecific electrocardiogram (EKG) changes to a severe form of cardiac injury known as neurogenic stunned myocardium or *takotsubo cardiomyopathy* [10]. 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 [11], which can present with cardiogenic shock. Typically, low ejection fractions on transthoracic echocardiogram (TTE) are detected that will improve in few days to a week on repeat echocardiogram. Cardiac enzymes can be elevated, but usually not as high as in the setting of an acute myocardial infarction. Subsequent levels tend to normalize on follow-up checks [12, 13]. Thus admission EKG, cardiac enzymes, and a TTE are warranted to detect and manage such complications.

Our patient's clinical presentation and radiological findings were classified as Hunt and Hess grade 4 and modified Fisher 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 nonspecific ST-T changes and the first set of cardiac enzymes were within normal limits.

On hospital day 5, the nurse mentioned that the patient's hourly urine output had increased by two to three times previous outputs. His sodium level on routine daily laboratory checks had dropped from 141 nmol/L to 133 nmol/L over 12 h.

What is the next step in the evaluation of his hyponatremia? What is its significance in aSAH 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 aSAH, occurring in about 30–40 % of patients [14]. Hyponatremia in aSAH patients increases the risk of cerebral vasospasm, DCI, and cerebral edema [15]. The most common etiologies for hyponatremia in this setting are cerebral salt wasting (CSW) or syndrome of inappropriate antidiuretic hormone (SIADH) secretion, both of which result in a hypotonic hyponatremia. It is challenging but important to differentiate between both causes of hyponatremia in patients with aSAH, as volume restriction therapy in patients with CSW misdiagnosed with SIADH will lead to intravascular depletion, which could precipitate or worsen cerebral vasospasm and secondary DCI. The pathophysiology of both syndromes is not entirely understood and it is not clear if both entities represent two ends of the same clinical spectrum [16]. SIADH is thought to be related to the excessive ADH release causing water retention and renin activity inhibition. This condition results in a euvolemic state with ongoing natriuresis [17]. A cerebrally induced salt wasting nephropathy is postulated to occur secondary to either impaired sympathetic input to the kidneys or release of natriuretic peptide following brain injury. Both pathologies lead to reduction of proximal sodium reabsorption and excessive natriuresis that will result in volume contraction [18]. CSW appears more commonly in aSAH with high clinical grade, ruptured Acomm aneurysm, and hydrocephalus [19, 20].

The first step in the *workup of hyponatremia* is to confirm that the drop in sodium level is not a laboratory error nor represents pseudohyponatremia, which is the case of

low sodium level in a setting of normal or high plasma osmolality (≥285 mOsm/kg). Hyperglycemia and hypertriglyceridemia will result in normal osmolality pseudohyponatremia, while mannitol administration will lead to low sodium with high osmolality [21].

The next key step in the evaluation of hyponatremia in aSAH patients is correctly identifying the extracellular fluid volume status of the patient, which is the main difference between CSW and SIADH [22]. Determining the fluid status of a patient is a challenging task even in an ICU setting. There is no validated single measure representing an accurate evaluation of a patient's fluid status rather than a combination of invasive or noninvasive methods. Hourly accurate measurements of input and output are recommended, which requires placement of an indwelling Foley catheter. Accurate and daily weights are also excellent measures of a patient's volume status. Most aSAH patients who receive hypertonic saline will require an intravenous central line access, of which a central venous pressure (CVP) can be obtained that could serve as an adjunctive measurement to guide fluid management; however, CVP is not proven to be a reliable reflection of intravascular volume [23]. Pulmonary wedge pressures (PWP) measured through inserted pulmonary artery (PA) catheters may have a role in hemodynamically unstable aSAH patients, yet the risks of PA catheter insertion may outweigh their benefit [24] and needs to be tailored to the needs of the individual patient. Other indicators of low volume status in patients includes decreased skin turgor, cool extremities, oliguria, low BP, and collapsible inferior vena cava at the end of expiration as observed on bedside cardiac echocardiography.

Patients with CSW are hypovolemic and are in negative fluid balance as compared to patients with SIADH that are euvolemic or have a positive fluid balance. Both syndromes will have almost similar laboratory workup that includes a serum osmolality <285 mOsm/kg, decreased serum uric acid levels, high urine osmolality (>200 mOsm/kg), and high urine sodium level (>40 mEq/L).

The management of hyponatremia in a setting of acute brain injury relies on the accurate diagnosis of the underlying syndrome. Care must be taken in correcting hyponatremia since too rapid a correction can lead to the development of an osmotic demyelination syndrome [25]. In aSAH patients at risk of cerebral vasospasm, it is recommended not to treat hyponatremia with fluid restriction even if SIADH is the underlying etiology [2] due to concerns of possible volume depletion leading to an increased risk of developing cerebral vasospasm.

Treatment of CSW relies mainly on administrating hypertonic saline as it has been shown to be superior to administrating normal saline in correcting hyponatremia [26]. Three percent hypertonic saline volume resuscitation improves the effect of CSW in aSAH patients at risk of DCI, improves regional cerebral blood flow (CBF) as well as the partial pressure of brain tissue oxygen tension in high clinical grade aSAH [27, 28]. Hyponatremia may develop rapidly in patients admitted with aSAH. Once hypertonic saline therapy is initiated, it is advised to check sodium levels every 4–6 h, in order to avoid quick overcorrection. Correction should occur at a rate no greater than 1–2 mEq/h, and no more than 10–12 mEq/L in the first 24 h. Fludrocortisone (Florinef) has been shown to reduce the risk of natriuresis and

cerebral vasospasm in patients with aSAH by improving the sodium levels and reducing the need for fluids [29, 30].

In patients with SIADH, fluid restriction less than 0.8–1 L per day is the mainstay of treatment, but it is not recommended in aSAH patients as mentioned previously. Normal saline infusion can worsen hyponatremia in SIADH if urine osmolality is higher than the infusate. Hypertonic saline with 3 % infusate should be administered in order to help raise the sodium levels in aSAH patients. Vasopressin receptors 2 (V2R) antagonists, such as conivaptan, promote aquaresis—water excretion devoid of sodium and potassium—helping raise the sodium level, especially in severe symptomatic hyponatremia. This may be useful in the aSAH patient that is volume overloaded and hyponatremic. Caution should be exerted to avoid rapid rise of sodium levels with use of V2R antagonists [31]. Oral salt tablets can be added to help promote urine output and to raise sodium levels, starting at 3 g 3 times a day [32].

On hospital day 7, the patient's neurological exam worsened as he stopped withdrawing his extremities to painful stimuli. A repeat head CT revealed unchanged hemorrhage burden and no change in the size of the ventricles. BP was 138/67, mean arterial pressure (MAP) of 91, and ICP readings ranged from 6 to 14. His daily transcranial Doppler (TCD) readings revealed elevated mean flow velocities (MFV) in his bilateral middle cerebral arteries (MCA), with MFV exceeding 200 cm/s, both of which were less than 140 cm/s the day prior. cEEG revealed slowing of the brain in the delta range without evidence of subclinical seizures.

What is the likely cause of the neurological exam worsening? What is the optimal BP parameter for such patients? What will be your next step?

One of the feared neurological complications in aSAH is symptomatic cerebral vasospasm. Vasospasm is defined as narrowing of the arteries in a setting of subarachnoid hemorrhage, as evidenced by angiography or sonography [33]. It commonly occurs between days 4–14 with a peak around day 7–8; however, early vasospasm has been reported in the first 48 h [34]. It is thought to occur as a result of the release of the inflammatory spasmogenic products from the subarachnoid hemorrhage covering the intracranial blood vessels. Only half of the patients that develop angiographic cerebral vasospasm become symptomatic, which can result in DCI due to reduced CBF and oxygen delivery [35]. DCI is a major cause of death and disability that has been shown to worsen patient's outcome [36]. Clinical manifestations of symptomatic cerebral vasospasm include global change in the level of consciousness or focal neurological deficits. Risk factors for cerebral vasospasm are higher clot burden and its proximity to the major intracranial vessels [37]. Oral *nimodipine* is recommended for aSAH patients. It is started on admission and continued for 21 days [6]. Interestingly nimodipine does not affect vessel narrowing but does appear to have an effect on overall outcome. The mechanism of this effect remains unclear but may be due to a direct neuroprotective effect [38]. BP decreases are not uncommon after oral nimodipine administration. This can potentially decrease a patient's cerebral perfusion pressure (CPP). A trial of nimodipine dosing changes to 30 mg every 2 h is suggested to help prevent such fluctuations. In some instances the medication may need to be discontinued or vasopressors added to support the patients' BP.

Cerebral autoregulation may be impaired in aSAH patients, putting the patients that develop hypovolemia and low BP at higher risk for developing vessel narrowing and subsequent DCI [39]. There are various monitoring techniques for the early detection of vasospasm including frequent neurological exams, CTA, CT perfusion (CTP), and digital subtraction angiography (DSA). Daily TCD studies provide a quick bedside noninvasive monitoring of elevated flow velocities in the large intracranial vessels, with good sensitivity and specificity as compared to DSA for early detection of vasospasm, especially when neurological assessment is unreliable in high-grade comatose aSAH patients [40].

The change in the neurological exam of our patient with the elevation of the MFV on TCD monitoring could be related to cerebral vasospasm in the absence of cerebral infarction. Prompt medical management with fluid administration and BP augmentation is the mainstay for treatment of the development of cerebral vasospasm. In the dysautoregulated brain, the aforementioned measures may improve CBF and subsequently the patient's neurological exam while awaiting further imaging to detect and treat ongoing vasospasm. Avoiding hypovolemia, and using invasive or noninvasive methods to detect the presence of vasospasm is crucial in aSAH patients. Studies have shown a relationship between hypovolemia and higher incidence of cerebral infarcts with worse outcomes in aSAH patients [41].

Prophylactic *triple H therapy* (hypertension, hypervolemia, and hemodilution) to prevent cerebral vasospasm, however, is not recommended [6]. Studies have shown no improvement in CBF, TCD-defined spasm, or clinical outcome in aSAH patients that are volume replete. Additional volume in this setting will increase the risk of systemic complications [42, 43].

Hemodynamic augmentation has been the mainstay of DCI management in conjunction with endovascular intervention. The goal is to improve CPP. CPP is calculated by MAP minus ICP. Normal saline bolus and intravascular volume expansion is a reasonable first step while initiating a vasopressor agent [2] as it has been shown to raise CBF in regions of the brain that are most vulnerable to ischemia [44]. Although aggressive fluid therapy and hypervolemia will raise the BP, fluid administration should be a judicious process, especially in patients with heart disease at risk of pulmonary congestion. Another risk with infusion of multiple liters of normal saline is the development of hyperchloremic metabolic acidosis that could also lead to renal impairment, especially in critically ill patients. It should then be considered to switch to other types of fluids, such as lactated Ringer's or colloids, with caution to avoid hyponatremia when using balanced solutions [45]. In recent studies by Suarez et al, albumin in higher dosages has been shown to be well tolerated in SAH patients and associated with less risk to develop TCD vasospasm and DCI [46]. Goal-directed fluid therapy (GDFT) has been shown to improve clinical outcomes and prevent DCI in patients with subarachnoid hemorrhage, especially in patients with high-grade SAH and undergoing surgical clipping surgery [47, 48]. GDFT includes use of cardiac output (CO), arterial pulse pressure variations (PPV), and stroke volume variation (SVV) monitoring. Following these dynamic parameters provides adequate intravascular volume status monitoring to provide appropriate CBF and ultimately cerebral oxygen delivery while avoiding the risk of fluid over-

load, which is equally important especially in vulnerable high-grade SAH patients with cardiac dysfunction. They have been shown to be accurate predictors of fluid responsiveness but unreliable in the patients with spontaneous breathing, cardiac arrhythmia, and right ventricular failure [49, 50].

Additional measures to improve cerebral oxygen delivery is transfusion of packed red blood cells (PRBCs) in anemic patients, with anemia being a risk factor for poor outcome in patients with subarachnoid hemorrhage. Although there is no consensus on a hemoglobin or hematocrit value threshold, it has been recommended to transfuse to a target above 8–10 g/dl [2], with 1 study showing safety of targeting a higher value of 11.5 in aSAH patients at high risk of vasospasm [51].

Induced hypertension is favored over triple H therapy (hypertension, hypervolemia, and hemodilution) to treat DCI and is commonly achieved by either norepinephrine or phenylephrine infusions. Vasopressors infusions should be titrated either to a certain percentage of MAP increase or in a step-wise increment to a certain blood pressure target. Serial neurological assessments can be used to monitor the effect of volume resuscitation or induced hypertension [52]. 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 has led to abandoning the practice of hemodilution [53].

An additional consideration to the hemodynamic augmentation in setting of DCI is the addition of inotropes agents to increase the cardiac output [54], especially in patients with high-grade SAH that developed neurogenic stunned myocardium and have evidence of low ejection fraction on their TTE. A few cases series have reported the use of intra-aortic balloon pump counterpulsation (IABP) to assist with the management of vasospasm, showing a potential in guiding the management of high-grade aSAH with cardiac dysfunction and neurogenic stunned myocardium that are at high risk of significant morbidity from myocardial infarction and pulmonary edema [55–57].

Hemodynamic augmentation should be followed as soon as possible by the evaluation of the cerebral vasculature with cerebral angiography for the treatment of symptomatic vasospasm using balloon angioplasty and/or intra-arterial vasodilators such as verapamil.

Conclusion

Our patient underwent blood pressure augmentation starting with a 1 L normal saline bolus, followed by the addition of norepinephrine drip titrated up slowly to detect improvement in his neurological exam. The patient's exam improved once his MAP was above 110 mmHg. He was subsequently taken to the angiography suite 2 h later. DSA showed evidence of moderate to severe cerebral vasospasm in the right MCA and anterior cerebral artery (ACA) territories, which required multiple injections of IA verapamil in the respective arteries with good response. The patients' exam improved and he required no further intervention.

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