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A Rational Approach to Perioperative Fluid Management

Daniel Chappell, M.D.,* Matthias Jacob, M.D.,* Klaus Hofmann-Kiefer, M.D.,* Peter Conzen, M.D.,† Markus Rehm, M.D.‡

Replacement of assumed preoperative deficits, in addition to generous substitution of an unsubstantiated increased insensible perspiration and third space loss, plays an important role in current perioperative fluid regimens. The consequence is a positive fluid balance and weight gain of up to 10 kg, which may be related to severe complications. Because the intravascular blood volume remains unchanged and insensible perspiration is negligible, the fluid must accumulate inside the body. This concept brings into question common liberal infusion regimens. Blood volume after fasting is normal, and a fluid-consuming third space has never been reliably shown. Crystalloids physiologically load the interstitial space, whereas colloidal volume loading deteriorates a vital part of the vascular barrier. The endothelial glycocalyx plays a key role and is destroyed not only by ischemia and surgery, but also by acute hypervolemia. Therefore, undifferentiated fluid handling may increase the shift toward the interstitial space. Using the right kind of fluid in appropriate amounts at the right time might improve patient outcome.

PERIOPERATIVE fluid application has been a topic of debate in past years. After the ongoing controversy on colloids *versus* crystalloids[1–3] and proposing the ideal composition of saline fluids,[4–7] the main focus is now on the amount of applied fluids in general.[8–13] The discussion is still dominated by the advocates of a more liberal regimen.[14–20] Most perioperative fluid overload is regarded as a minor problem, and studies showing increased fluid accumulation in tissue have not changed this attitude.[21,22] Rather, preoperative volume loading is considered indispensable by many,[15,19,23–26] and fluid boluses are part of most recommendations for perioperative care.[11,27] This statement is mainly based on four generally unquestioned pathophysiologic "fundamentals": (1) The preoperatively fasted patient is hypovolemic because of ongoing insensible perspiration and urinary output[10]; (2) the insensible perspiration increases dramatically when the surgeon starts cutting the skin barrier[27]; (3) an unpredictable fluid shift toward the third space requires generous substitution[28]; and (4) hypervolemia is harmless because the kidneys regulate the overload.[29]

The purpose of this review is to promote a rational perioperative fluid management, combining common knowledge with clinical research results and new physiologic insights regarding the vascular barrier. This review will explain and underline the importance, quantity, and destination of perioperative fluid shifting and its related problems.

Perioperative Fluid Optimization: Do All Roads Lead to Rome?

The attending anesthesiologist is faced daily with several principal and practical problems when arranging perioperative fluid handling. Under normal circumstances, the individual patient's hydration and volume state before surgery is unknown. In addition, the exact target remains unclear, and many theoretically possible targets cannot be measured in clinical routine. The principal goal is to optimize cardiac preload. An important determinant, total body blood volume, should be optimized to achieve this. Importantly, *optimizing* does not necessarily mean *maximizing*, despite frequently being interpreted in this way,[30] and blood volume cannot be assessed routinely: Double-label blood volume measurement, the current standard to assess total body blood volume, is invasive, complex, and personnel intensive.[31–34] Alternative methods that do not use sampling lack calibration and are, therefore, imprecise.[35] Hematocrit dilution is often based on estimated basic values and can only assess changes in the circulating part of the blood volume,[33,36,37] ignoring a considerable noncirculating portion of the plasma (see section titled The Endothelial Glycocalyx: The Gateway to the Interstitial Space). Therefore, direct blood volume measurements are possible in principle and are frequently used to answer scientific questions. Unfortunately, they remain impractical in everyday routine.

Measuring volume responsiveness, occasionally referred to as a "goal-directed" approach,[30,38,39] seems at first to be an interesting alternative to directly measuring blood volume, but it has several limitations. First, there is no proof that this circulatory surrogate, enabling the clinician to maximize stroke volume, really achieves the optimum. Second, the two still most applied measures in this context, *i.e.*, pulmonary capillary wedge pressure and central venous pressure, do not at all predict volume responsiveness, in clear contrast to the common assumption.[40,41] Systolic pressure and pulse pressure variation, on the contrary, predict volume responsiveness, but do not improve patient outcome.[38] Stroke volume maximization *via* esophageal Doppler-guided fluid boluses seems to improve outcome,[30] especially in elderly and frail patients.[39] This method, however, cannot be performed everywhere and in every patient for practical and

* Staff Anesthesiologist, † Professor of Anesthesiology, ‡ Associate Professor of Anesthesiology.

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Address correspondence to Dr. Jacob: Clinic of Anesthesiology, Ludwig-Maximilians University Munich, Nussbaumstrasse 20, 80336 Munich, Germany. matthias.jacob@med.uni-muenchen.de.

financial reasons. Performing esophageal Doppler measurements in awake patients, to apply a rational fluid regimen from the very beginning of the anesthesiologic procedure, is almost impossible. Moreover, it has up until now been compared with only standard fluid handling, which revealed no large differences between the total fluid volume of the two studied groups.[30,42] Accordingly, assuming the worst case, the actual message behind these data could also be that esophageal Doppler-guided fluid overload is superior to uncontrolled fluid overload. But this message does not answer current questions regarding alternative concepts.

"Liberal," "Standard," or "Restrictive": It's in the Eye of the Beholder

Results of studies on fluid therapy will have an impact on everyday practice only if clinicians are able to accept one or more alternative regimens as being superior. Many clinicians are reluctant to change their fluid practices, impeding research on perioperative fluid handling and acceptance of protocol-based improvements. Research suffers not only from an almost unascertainable target, but traditionally from a lack of standardization, complicating the design of control and study groups. Investigators have normally named their traditional regimen the *standard* group and compared it with their own restrictive ideas. Consequently, a *restrictive* regimen in one study is often designated as *liberal* in another setup. In addition, studies claiming to compare restrictive *versus* liberal use of fluid should, in part, rather be interpreted as investigating hypovolemia *versus* normovolemia.[13] This shortcoming prevents even promising results from impacting daily clinical routine and makes any pooling of the data impossible. A further important limitation of the data in this field is the target of a given study. Perioperative fluid handling has been related to, among other things, nausea and vomiting, pain, tissue oxygenation, cardiopulmonary disorders, need of revision surgery, duration of hospital stay, and bowel recovery time. However, the relevance of each individual target depends on the examined type and extent of surgery, which in turn has an enormous influence on changes and significance of these outcome parameters. Avoiding postoperative nausea and vomiting (PONV) in cardiopulmonary-healthy patients, for example, might be the most important goal after a 15-min knee arthroscopy. By contrast, it is merely a minor issue after a 6-h major abdominal intervention, in which cardiopulmonary complications or mortality rates are in the spotlight. Therefore, a careful differentiation between large and small operations, as well as abdominal *versus* nonabdominal surgery, seems to be necessary.

Major Surgery

Even though the results of several studies regarding major nonabdominal surgery are currently underpowered and partly inconclusive,[43] the findings in patients receiving major abdominal surgery are quite promising. It has been demonstrated that protocol-based fluid restriction reduced the incidence of perioperative complications such as cardiopulmonary events[8,11] and disturbances of bowel motility,[11,44] while improving wound and anastomotic healing[8,11] and reducing hospital stay.[11,44] Lobo *et al.*[44] investigated 20 adults after elective colonic resection. Intraoperative fluid application was quite aggressive (20 ml · kg^{-1} · h^{-1}) in all patients, but postoperatively, they were randomly assigned to either a restrictive ($\leq$ 2 l per day) or a standard ($\geq$ 3 l per day) protocol. The latter caused a significant weight gain, a later return of bowel function, and a prolonged hospital stay. It seems as though not only intraoperative but also postoperative fluid management can have an impact on patient outcome. In a larger trial of 80 patients undergoing colorectal surgery, MacKay *et al.*[45] did not confirm these findings, despite their protocols for postoperative fluid management seeming, at first, comparable. However, a decision analysis reveals any comparison between these two studies to be difficult: Patients of both randomization groups were intraoperatively treated with relative fluid restriction (basal rate 10 ml · kg^{-1} · h^{-1}) compared with the work of Lobo *et al.*[44] (approximately 18 ml · kg^{-1} · h^{-1}). This is clearly reflected by the postoperative weight gain, an indirect measure for the interstitial fluid shift. The patients in the restrictive group of MacKay *et al.* had a body weight decrease of 0.5 kg, whereas the increase in their liberally treated group (+0.7 kg) was even less than that of the restrictive group of Lobo *et al.* (+1.1 kg). Above that, a sufficient postoperative fluid balance is not possible, because oral fluid intake was only "encouraged"[45] and not reported by McKay *et al.* Nevertheless, with no patient receiving more than 3 l intravenous fluid a day, even perioperatively, most likely even their standard group was treated too restrictively to cause measurable harm. These findings underline the importance of a rational concept comprising the entire perioperative treatment.

In a multicenter study, Brandstrup *et al.*[8] investigated a homogenous collective of 141 patients undergoing major colorectal surgery. They demonstrated that perioperative intravenous fluid restriction (mean 2,740 *vs.* 5,388 ml) significantly reduced the incidence of major and minor complications, such as anastomotic leakage, pulmonary edema, pneumonia, and wound infection. Despite limited fluid application and a perioperative decrease in urine output, acute renal failure did not occur in any patient. However, Brandstrup *et al.* did not purely compare liberal *versus* restrictive, but, as a close look at the infusion protocols reveals, colloids *versus* crystal-

loids, applying mainly colloids to the restrictive group while treating the liberal group with more than 5 l crystalloids.[8] Nisanevic *et al.* found decreased postoperative morbidity, including a shortened hospital stay, under a protocol-based, more restrictive fluid therapy (1.2 *vs.* 3.7 l) in a more heterogeneous collective consisting of 152 patients scheduled to undergo mixed abdominal surgery.[11]

As a conclusion of a systematic review of 80 randomized clinical trials, Holte and Kehlet[43] recently recommended avoiding "fluid overload in major surgical procedures."

On the other hand, there is also the point of view that liberal fluid therapy has beneficial effects on various outcome parameters. In the following passages, we examine these assertions more carefully.

Postoperative Nausea and Vomiting

Maharaj *et al.*,[19] for example, reported large fluid amounts during laparoscopic surgery to decrease pain and PONV. However, their restrictively treated group received only 212 ml fluid perioperatively after a fasting period of 13 h. The patients with an increased incidence of PONV might not have received an adequate fluid replacement therapy to restore their extracellular compartment. Above that, 65% of the restrictively treated patients received morphine (*vs.* 35% in the liberally treated group) before hospital discharge, which itself is known to increase the risk of PONV.[46] Furthermore, this could mean that large fluid amounts have the potential to decrease postoperative pain, an important additional effect in this collective. Magner *et al.*[47] found comparable beneficial effects on the incidence of PONV after a 19-min laparoscopic intervention, having infused 1,900 ml within this short period of time. Holte *et al.*,[48] however, relativized this aggressive approach by demonstrating such, at first view, beneficial effects after knee surgery to be related to a decreased coagulation state and postoperative weight gain, which was still existent 72 h after surgery. During laparoscopy, however, they found a liberal fluid handling (40 *vs.* 15 ml/kg) to decrease PONV and to improve postoperative lung function. An observed increased release of atrial natriuretic peptide,[17] which might crucially influence the vascular barrier function (see section titled Perioperative Protection of the Endothelial Surface Layer), did not seem to be related to measurable harm after minor surgery. On the other hand, McCaul *et al.*[49] showed that even a complete lack of any perioperative infusion did not increase the risk of PONV compared with infusing 1.1 l compound sodium lactate.

These data, despite being inconsistent, indicate that higher fluid amounts might reduce the risk of PONV and increase postoperative lung function after short operations. Nevertheless, most studies considered only one outcome parameter; therefore, the overall effect on the patient is hard to gauge, because other, potentially more serious parameters may be impacted adversely by the same treatment. These results seem interesting regarding certain collectives, *e.g.*, outpatients during minor surgery, but they cannot account for larger surgery over several hours. Current evidence suggests that liberal fluid is a good idea where major trauma and fluid shifting are unlikely, but more careful fluid management may be beneficial in more stressful operations.

Wound Infection and Tissue Oxygenation

Wound infections are serious complications of surgery. Oxidative killing by neutrophils is the most important defense against pathogens causing surgical infections.[50] Because oxygen is the substrate for oxidative killing, the rate of bacterial killing depends on sufficient tissue oxygenation. Therefore, the risk of surgical wound infection is inversely related to tissue oxygenation,[51] which is also an important substrate for tissue repair and wound healing,[52,53] and influenced by various factors: Mild hypothermia triples the risk of infection by reducing tissue oxygenation, but conversely, supplemental perioperative oxygen halves the risk of infection by increasing tissue oxygenation.[54] However, even supplemental oxygen does not improve oxygenation in hypoperfused tissues.[51] Therefore, adequate perfusion is required for rapid healing and optimal resistance to infection. Obviously, it is important to perioperatively maintain an adequate blood volume,[13] being, in principle, defined as a blood volume enabling the circulation to sufficiently perfuse the tissues. In practice, adequate volume is usually defined by hemodynamic stability, because there is no routine clinical method for evaluating tissue perfusion. Because hypovolemia does not only reduce peripheral tissue perfusion before compromising blood pressure, increasing heart rate, or reducing urine output,[55] it is evident how important it is to avoid hypovolemia.

Several studies during major abdominal surgery postulate that "aggressive fluid administration" increases tissue oxygenation.[53,55] Because potential danger resulting from crystalloid overload was not well studied until very recently, liberal fluid handling has been traditionally recommended by many textbooks. Unfortunately, the underlying studies have several shortcomings. Mostly, tissue oxygenation was the only reported outcome parameter; weight gain, edema formation, anastomosis healing, coagulation factors, hospital stay, bowel function, renal failure, and cardiopulmonary complications—all well-known effects of excessive fluid overload[8,11,44]—were not measured. Above that, in most studies, patients received bowel preparation the day before surgery, which is currently questioned,[56,57] and fasted for more than 8 h, which also is not in accordance with current guidelines.[58,59] De-

spite the fact that fasting alone only slightly decreases extracellular fluid but maintaining intravascular normovolemia,[60] a combination with preoperative bowel preparation is suspect to induce a significant intravascular deficit.[9,10] Therefore, most of the study patients were likely to be hypovolemic.[61] Applying 2.1 *versus* 3.8 l crystalloids during major abdominal surgery (including the preoperative phase) after fasting and bowel preparation does not seem to be the intended conservative *versus* aggressive fluid therapy, but rather a too restrictive *versus* adequate regimen.[53] What crystalloid overload could mean to the tissues was illustrated more than 30 yr ago by an animal experiment. Infusion of 10 ml/kg isotonic saline solution in rabbits significantly decreased tissue oxygen tension for 3.5 days.[62] In a recent study from Kabon *et al.*,[63] patients receiving bowel preparation had substitution of 2 ml · kg^{-1} · h^{-1} overnight, and then 2.5 and 4.6 l crystalloid administration during major abdominal surgery were compared. No improvement of wound infection or wound healing was found after colorectal surgery in the "aggressively" treated group. Recently, Kimberger *et al.*[64] showed that tissue oxygen tension can be increased by supplemental oxygen but not by supplemental crystalloid fluid, whereas Hiltebrand *et al.*[65] found no augmentation in tissue oxygen pressure by high *versus* medium or low fluid regimens. While these are experimental data from animals with various limitations, recent evidence suggests that aggressive fluid therapy can be detrimental even in humans. Nisanevich *et al.*[11] reported a higher rate of infectious complications (including surgical site infection) and a longer hospitalization period for the group receiving a large volume of fluids.

Moreover, epidural anesthesia[66,67] and mild hypercapnia[68,69] have been shown to increase subcutaneous tissue oxygenation. Sufficient tissue perfusion has been shown to have a benefit on survival in high-risk patients and depend on a higher mean arterial pressure, cardiac index, and mixed venous oxygen saturation, as well as significantly higher oxygen delivery and oxygen consumption.[70] Intravascular volume replacement with colloids (hydroxyethyl starch 130/0.4) has been shown to reduce the inflammatory response in patients undergoing major surgery compared with a crystalloid-based volume therapy.[14] This has been interpreted to be most likely due to an improved microcirculation with reduced endothelial activation and less endothelial damage.[18]

Because of a total lack of standardization, the available data do not allow evidence-based recommendations on practical perioperative fluid management.[43] Any perioperative fluid handling seems to be justified. However, this is in clear contrast to daily clinical observations during surgery, suggesting that our various surgical and anesthesiologic standard treatments might contribute to important perioperative problems.

Fluid Shifting: A Relevant Perioperative Problem

Fluid shifting out of the vasculature depends, in principle, on the body core temperature. Below 30°C, a significant decrease of plasma volume, accompanied by a decrease of central venous pressure, an increase of pulmonary and systemic resistance, and an increase of hematocrit have been reported.[71] Between 37° and 33°C, however, no significant dependence on body temperature has been observed. Accordingly, this should not be a frequent intraoperative problem in noncardiac surgery. Nevertheless, fluid shifting is an often recognized phenomenon during and after surgical procedures. Direct and indirect blood volume measurements have shown that major surgery causes a deficit of 3–6 l in the sensible perioperative fluid balance,[31,32,34,72] *i.e.*, measurable input (crystalloid and colloid) minus measurable output (blood loss and urine output; fig. 1). This shift is not only an intraoperative but also a postoperative problem. The peak of fluid shifting has been reported to be at 5 h after trauma and to persist for up to 72 h, depending on the location of the operation site and on the duration of surgery.[73] Lowell *et al.*[74] found that 40% of patients admitted to a surgical intensive care unit had an excessive increase in body water of more than 10% from preoperative weight. Extracellular volume (ECV) overload has been shown to exceed 10 l after 2 days of resuscitation in patients with sepsis. This fluid storage was obviously trapped inside the body and needed 3 weeks to be excreted.[75] Above that, even in healthy volunteers, it has been demonstrated that it takes 2 days to completely excrete a saline infusion of 22 ml/kg.[76,77] One week after fluid resuscitation with 3–7 l fluid in patients with burns, only half of the patients had eliminated this infusion.[78] But not only the fluid shift out of the vasculature seems to be dangerous for patients. Also, fluid reabsorption can result in cardiac overload, occasionally leading to acute cardiac failure and pulmonary edema.[79]

Perioperative weight gain, being the most reliable marker of fluid storage outside the circulatory space, has been shown to be strongly related to patient mortality in a retrospective study of patients not randomly assigned to distinct fluid infusion regimens: In patients who gained less than 10% body weight, mortality was 10%; in patients whose body weight increased between 10% and 20%, mortality was 32%; and in patients whose body weight increased by more than 20%, mortality was 100% (fig. 2).[74] An unanswered question in this context is whether fluid shifting was a cause or an effect. However, the study impressively illustrated what was going on in the operating rooms of the late 1980s and what still frequently happens to patients in 2008. The operations investigated here were associated with severe trauma and blood loss. Nevertheless, the patients were treated

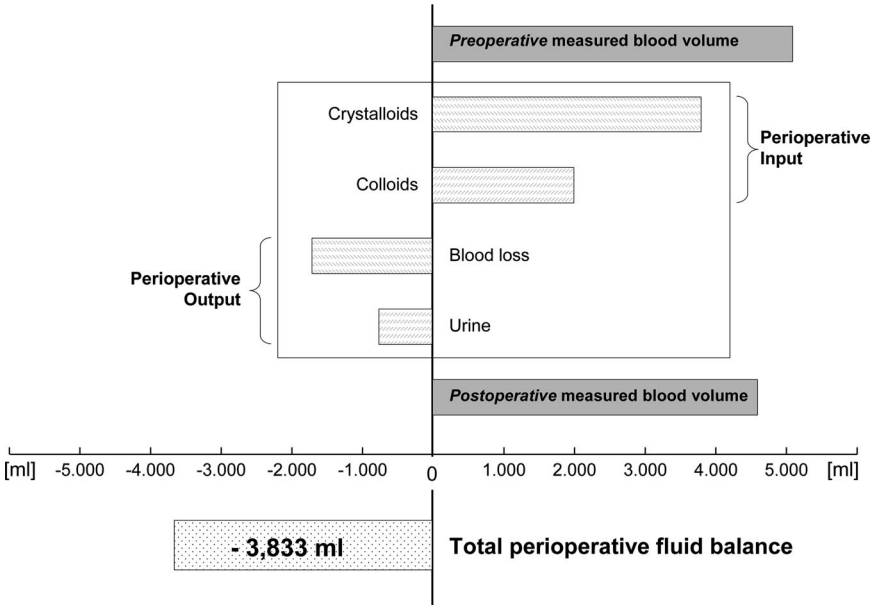

Fig. 1. Median blood volume status of 13 patients with ovarian cancer before and after major abdominal surgery, receiving a standard infusion regimen (crystalloids: approximately 12 ml · kg^{-1} · h^{-1}; iso-oncotic colloids: blood loss replacement in ratio 1:1). Direct blood volume measurements (double-label technique) revealed a perioperatively occurring, at first unexplainable fluid loss out of the circulation.[97] Median values (range): Preoperative blood volume 5,104 (4,099–6,004) ml, crystalloid infusion 3,800 (800–8,000) ml, colloid infusion 2,000 (0–4,700) ml, blood loss 1,700 (100–3,800) ml, urine production 750 (100–1,950) ml, postoperative blood volume 4,621 (3,802–5,170) ml. Total perioperative fluid balance is calculated from the measured parameters.

with large amounts of crystalloids and—if necessary—blood products. This means that a loss of colloid osmotic force was not sufficiently replaced. Patients with a relative low crystalloid infusion (4.1 l) had a weight gain of 4.7%, 1.7 days of postoperative ventilation, a vasopressor dependence of 2.8 days, and a mortality of 10%. In the group receiving "aggressive"[74] fluid resuscitation (12.5 l crystalloids), weight gain accumulated to 31.7%, 6 days of postoperative ventilation were required, and 26 days of vasopressors therapy were necessary. Mortality was 100%. In this group, despite an excessive fluid supply, 33% developed acute renal failure (*vs.* 17% in the low fluid group). Also, invasive monitoring and postoperative ventilation correlated with the amount of infused fluids and the postoperative weight gain. Nevertheless, the authors stated that it was "almost certainly true that in many instances excessive volume was administered."[74] Other studies have shown a positive fluid balance in critically ill patients to be a common problem in the unit and to often be associated with poor outcome, such as increased mortality and prolonged intensive care treatment dependency and ventilator dependency.[80–82] Aggressive crystalloid infusion has been demonstrated to impede oxygen consumption, whereas lower infusion rates may provide better oxygen delivery with less increase of interstitial fluid accumulation.[83] A mean total applied amount of 12.5 l crystalloids, in combination with only 500 ml iso-oncotic colloid, but 18 units packed erythrocytes indicate a very hypooncotic therapy of an obviously excessive blood loss. Possibly, the patients would profit from a more colloid-accentuated resuscitation strategy, improving oxygen delivery and oxygen consumption by limiting extracellular fluid storage.[83]

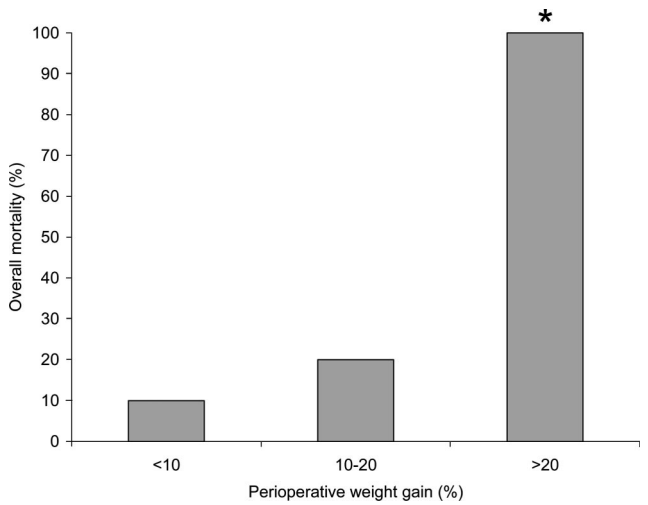

Fig. 2. Perioperative weight gain and mortality of patients. No patient survived if perioperative weight gain was more than 20%.[74] * $P < 0.008$ *versus* weight gain less than 10%.

The corresponding "crystalloid *versus* colloid" debate has been enlarged by a "colloid *versus* colloid" controversy during the past years,[84] and one should obviously carefully distinguish what kind of colloid to use for which indication. Unfortunately, large randomized studies reliably comparing the two main colloids of interest, human albumin *versus* a modern, third-generation hydroxyethyl starch preparation, remain eagerly expected. The data regarding colloids *versus* crystalloid are contradictory. Hankeln *et al.*[85,86] compared the cardiopulmonary effects of lactated Ringer's solution and 10% hydroxyethyl starch in 15 critically ill patients. Using the artificial colloid produced a significantly increased cardiac index, left and right ventricular stroke work index, central venous and wedge pressure, oxygen delivery, and oxygen consumption. Pulmonary vascular resistance index was reduced. The highly cited recent study by the investigators of Volume Substitution and Insulin Therapy in Severe Sepsis comparing 10% pentastarch (hydroxyethyl starch 200/0.5) with lactated Ringer's for resuscitation in

severe sepsis, by contrast, was stopped early because of a significant increase in acute renal failure in the group receiving hydroxyethyl starch.[87] A careful look at the study design, however, reveals that, irrespective of whether bleeding occurred, a second-generation hypertonic hydroxyethyl starch at a total amount clearly beyond the recommended dose was applied. A subgroup analysis of low-dose ($\leq$ 22 ml/kg) *versus* high-dose ($>$ 22 ml/kg) application revealed a significantly lower mortality (31% *vs.* 58%), even compared with crystalloid resuscitation (41%). Therefore, any conclusion drawn from these data regarding the use of hydroxyethyl starches in general should be made with caution. Nevertheless, these preparations are well known to induce severe side effects including pruritus, pleiotropic effects on the coagulation system, including reductions in coagulation factor levels, a decrease in number and function of platelets, and increased fibrinolysis.[88] These effects, however, are clearly related to cumulative dose, mean molecular size, and substitution degree of the respective preparation.[89,90]

The use of human albumin *versus* crystalloid for fluid resuscitation did not improve outcome in 6,997 critically ill patients.[91,92] In the subgroup of patients with traumatic brain injury, it actually increased mortality.[93] Patients do not seem to inevitably benefit from colloid resuscitation if they do not experience bleeding or acute protein loss from the vasculature.[94]

Generally, substantially more crystalloid is necessary to effect equivalent changes in hemodynamics. High-volume crystalloid resuscitation reduces oncotic pressure and may predispose to pulmonary[95] and peripheral edema, which interferes with tissue oxygen exchange and delays wound healing.[96] However, not only crystalloids are shifted out of the vasculature, but also colloids (see section titled Crystalloid *versus* Colloid: Time to End an Erroneous Discussion).[33,97]

This discussion raises several questions: Where does the body store this shifted fluid? Is it an interstitial shift or located within the mysterious third space? Does this space primarily consume fluid during major surgery which has to be replaced[98]— or is fluid overload rather the trigger for such an occurrence? A small physiologic excursion into the mystic world surrounding the third space might provide some answers to these questions.

Interstitial or Third Space?

The third space has systematically been divided into an anatomical part and a nonanatomical part.[99,100] Anatomical losses are considered to be a physiologic phenomenon at a pathologic amount, *i.e.*, pathologic fluid accumulations within the interstitial space, the "functional" ECV (fECV). Physiologic fluid shifting with an intact vascular barrier from the vessels toward the interstitial space is considered to contain only small amounts of protein and only small molecules.[101] As long as it is quantitatively managed by the lymphatic system, a physiologic shift does not cause interstitial edema.[102] Overwhelming the lymphatic system, *e.g.*, *via* excessive application of crystalloids, does. However, this problem can principally be resolved contemporarily *via* redistribution and urinary output.

Nonanatomical third space losses formally represent a fluid compartment functionally and anatomically separated from the interstitial space.[98,103,104] Therefore, fluids trapped within this compartment are considered to now be part of the "nonfunctional" ECV (nfECV).[105] Losses toward this classic third space have been described as a fluid accumulation caused by major surgical procedures or trauma in spaces normally containing no or little fluid. Identified examples are the peritoneal cavity, the bowel, and traumatized tissues, but other, nonlocalized compartments are also postulated by the experts. Although total body water primarily remains unchanged by this theory, the "nonfunctional" part of extracellular fluid increases at the expense of the "functional" one. At least on the scene, this part is believed to be lost for extracellular exchange; it is unable to participate in the extracellular dynamic equilibrium.

Third Space: Quantification

Despite an intensive search for the perioperatively lost fluid, it is not localized in "nonanatomical" spaces: Neither the gut[106] nor traumatized tissue[107] contain these high amounts of fluid. Classic third space fluid losses have never been measured directly, and the actual location of the lost fluid remains unclear.[103] Therefore, these losses have been merely quantified indirectly by repeatedly measuring perioperative changes in the fECV *via* tracer-dilutional techniques,[103,108] presuming that the total ECV (functional plus nonfunctional) remains constant. These techniques are based on the principle of applying a known amount of a "suitable" tracer into a certain fluid compartment of the body. The concentration of the tracer within this compartment after a "suitable" equilibration interval leads to the distribution volume. The nfECV, however, is an ill-defined space, and high demands are made on a tracer to label fECV. On one hand, it must pass through the capillary wall membrane, but on the other hand, it must be excluded by the body's cell membranes, thus, making it extremely difficult to produce exact measurements. Such procedures, therefore, are limited by three main questions identifying three major shortcomings of tracer dilution when applied to fECV measurements: What is a suitable tracer distributing exclusively within the fECV? What is a suitable equilibration interval, allowing complete distribution, but not interfering with redistribution or tracer-

elimination kinetics? And, finally, how can a method to quantify fECV be reliably validated?

Despite these concerns, different tracers, techniques, sampling times, and mathematical calculations of the fECV have been used, leading to different results and various conclusions. It seemed that only trials using the sulfate tracer $^{35}SO_4$ with a relatively short equilibration time and calculating the fECV from a single or very few blood samples have reported a third space loss during surgery or hemorrhagic hypotension.[109–112] Adequate equilibration times to measure fECV have, however, been reported to be up to 3 h for the sulfate[113] and over 10 h for bromide (^{82}Br),[114] the most common tracers. Problems of these tracers are that bromide enters erythrocytes and is excreted in bile,[115] whereas sulfate is bound to plasma components[116] and accumulates in the liver, in the kidneys, or during shock in muscular tissue.[113,117] Above that, the necessary time for a tracer to achieve equilibration has been shown to be prolonged after surgery,[104,118] hemorrhagic hypotension,[104,118–120] and fluid overload.[121] Single measurements will produce too-low or too-high plasma concentrations, overestimating or underestimating the calculated volume distribution if not taken at the exact equilibration time. Therefore, it is recommended to calculate tracer spaces from continued multiple samples until equilibration is shown in each individual case.[108,122] Above that, a prerequisite for using tracer kinetics for volume measurements is a steady state condition, hardly given during shock or surgery.[106,108,111,122] Surprisingly, trials using multiple blood samples after longer equilibration times to measure the fECV all found the opposite of a third space loss: After surgery, an unchanged or even increased fECV was detected.[104,106,111,114,118,123–133] Trials using the bromide tracer all found an fECV expansion after surgery, unaccounted for by the calculated fluid balance.[114,118,123,124,127,128] Accordingly, and in contrast to the common assumption, the majority of the data do not support the existence of a third space.

In summary, a classic third space was never localized and only "quantified" with one specific method using certain conditions regarding sampling and equilibration times, implying serious concerns and weaknesses.[104,119,128,134] All other methods using various tracers, multiple sampling techniques, longer equilibration times, or analysis of kinetics contradict the existence of a fluid-consuming third space.[104,114,118,123,124,128,129,133,135–139] Taking all this into account, we have to conclude that a classic third space *per se* quantitatively does not exist. It is currently not more than an ill-defined compartment thought to reflect an otherwise unexplainable perioperative fluid shift. Therefore, we suggest abolishing this mystery and sticking to the given facts: Fluid is perioperatively shifted within the functional extracellular compartment, from the intravascular toward the interstitial space.

Perioperative Fluid Shift: Trigger or Effect of Liberal Fluid Handling?

Currently, it seems unclear whether high infused amounts of fluid are the cause or the effect of an occurring shift toward the interstitium. In particular, it is still not known whether surgery and trauma cause the main part of an impressive primary fluid shift outward that must be treated with high amounts of fluid or whether, rather, an overwhelming infusion therapy causes severe perioperative problems that should be avoidable for the anesthesiologist. An interesting animal study performed more than 20 yr ago gave an important clue.[100] It was demonstrated in a rabbit model during enteral anastomosis that the surgical manipulation itself is enough to cause a significant increase of the interstitial water load by 5–10%, without any infusion therapy. An accompanying crystalloid infusion of 5 $ml \cdot kg^{-1} \cdot h^{-1}$ doubled this edema. Surgery and trauma *per se* obviously have the power to cause a certain extent of fluid shifting, whereas crystalloid infusion therapy impressively influences its extent.

The following will further explore the interesting possibility that current liberal fluid therapy, in addition to surgery, is related to a significant perioperative imbalance of fluid homeostasis.

The Physiologic Background

Intracellular fluid comprises two thirds of the body water. The remaining one third, approximately 15 l in the normal adult, designates the ECV, consisting of the plasma (approximately 3 l), the interstitial space (approximately 12 l), and small amounts of so-called transcellular fluids, such as gastrointestinal secretion, cerebrospinal fluid, and ocular fluid.[103,140] Because the latter fluid compartments are obviously, even under physiologic conditions, anatomically separated and not in a dynamic equilibrium with the other two parts, they are considered to be "nonfunctional." By contrast, the interstitial space and the plasma represent the "functional" extracellular space,[98,103] in which water and small solutes can easily exchange, a prerequisite for cell nutrition.

Fluid distribution within the human body is related to the distribution of osmotic active substances. The physiologic distribution is maintained by biologic barriers and oxygen-consuming ion pumps. The intact vascular barrier cannot be crossed by large molecules and proteins in relevant amounts.[141] This is important because it enables the circulation to generate a positive intravascular blood pressure without unlimited fluid loss toward the interstitial space. Ernest Starling, a British physiologist, introduced his underlying classic model of the vascular barrier as early as 1896: Inside the vessels, the hydrostatic pressure is high, as is the colloid osmotic pressure.[142] In contrast, according to this model, the

interstitial space contains a low amount of proteins, whereas the hydrostatic pressure there is also low (fig. 3). The theoretical net result is a low filtration rate per unit of time, assembling to:

$$J_v = K_f([P_c - P_i] - \sigma [\pi_c - \pi_i]),$$

where J_v = net filtration; K_f = filtration coefficient; P_c = capillary hydrostatic pressure; P_i = interstitial hydrostatic pressure; σ = refection coefficient, π_c = capillary oncotic pressure; and π_i = interstitial oncotic pressure.

Accordingly, a sufficient plasma protein concentration should be necessary to provide a physiologically active inward directed force to successfully oppose the hydrostatic pressure gradient. Nevertheless, a small net fluid and protein shift out of the blood vessels occurs all the time, but is disposed in a timely manner from the interstitial space *via* the lymphatic system under physiologic conditions.[143]

According to this model, crystalloid overload should only cause a moderate fluid shift toward the interstitial space. The resulting increase in interstitial hydrostatic pressure, together with a dilution of the interstitially stored proteins, has been interpreted as an important edema-limiting mechanism.[144] An accompanying increase in lymph flow in addition limits interstitial fluid volume expansion despite extracellular overload.[102] Transfer of a substantial amount of the interstitial protein pool back into the vascular compartment by this increased lymph flow further contributes to this incident, increasing the inward-directed oncotic gradient.[102] Surgery-induced inflammation, on the contrary, is believed to cause inevitable interruption and impediment of the reabsorption and return of the fluid to the circulation *via* the lymphatics.[145] This must derange the physiologic compensation and requires an intravascular fluid replacement by the anesthesiologist to maintain normovolemia and, therefore, cardiac preload. But does this way of thinking really reflect current physiologic knowledge? And is it really adequate to generalize fluids without distinguishing between crystalloids and colloids? A systematic look at perioperative losses and recent findings regarding the vascular barrier might help to answer this question.

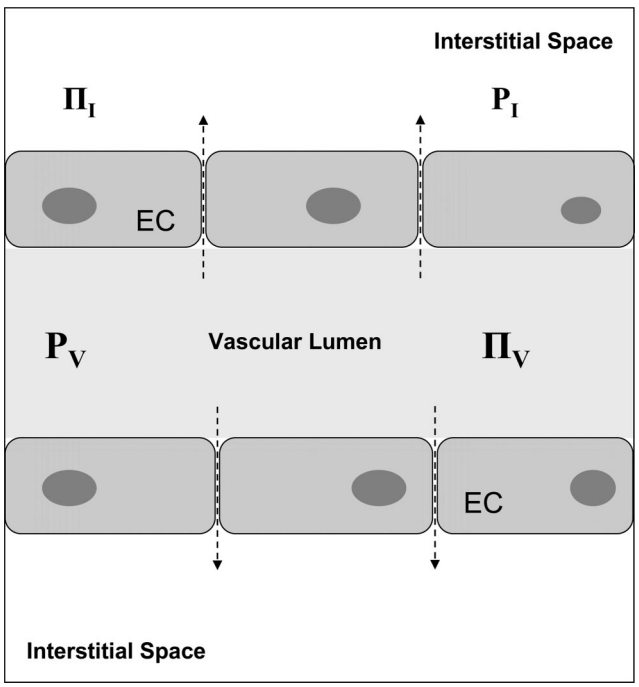

Fig. 3. The classic description of vascular barrier functioning in arterioles and capillaries, according to Ernest Starling (schematic): An inward-directed colloid-osmotic (= oncotic) pressure gradient is opposed to an outward-directed hydrostatic pressure of fluid and colloids. The *arrows* symbolize the small net fluid filtration assumed according to this model. The extremely simplified illustration does not consider the postulated small net fluid reabsorption on the venular site suggested by this model, due to an assumed decrease in the hydrostatic and an assumed increase in the oncotic pressure gradient. The Starling equation is mentioned in the main text. Π_I = oncotic pressure in the interstitial space; Π_V = oncotic pressure in the vascular lumen; EC = endothelial cell; P_V = hydrostatic pressure in the vascular lumen; P_I = hydrostatic pressure in the interstitial space.

Mechanics of Perioperative Fluid Handling

Perioperative fluid application basically must replace two kinds of losses: (1) losses occurring all the time (mainly urine production and insensible perspiration), possibly to another extent than under "normal" conditions; and (2) losses occurring exclusively during trauma and surgery (mainly blood losses). The first kind of loss affects the entire extracellular space, *i.e.*, the intravascular plus the interstitial space, and normally does not lead to a loss of colloid osmotic force from the intravascular space. The second loss induces a primarily isolated intravascular deficit, including losses of all blood components. In practice, we only have access to the vascular space, even when treatment of the entire extracellular compartment is intended.

Extracellular losses *via* urinary output and insensible perspiration are, schematically, replaced by absorption of colloid-free fluid and electrolytes from the gastrointestinal system. In the fasted patient, this compensation mechanism fails and has to be imitated artificially by the anesthesiologist. Theoretically, the best solution is an application of crystalloids, ideally in a balanced form, as not to cause acid–base disorders.[146] Because crystalloids are not retained at the vascular barrier after having been infused intravenously, they are homogenously distributed within the extracellular space, *i.e.*, four fifths are distributed into the interstitial space. Only one fifth remains intravascularly.

When substituting acute blood losses, there is no physiologic correlate we try to imitate, and each regimen must remain extemporaneous. Theoretically, an isovolemic online transfusion of warm whole blood should be considered

optimal, because this is what is actually lost. Such an approach, however, is not an ideal target for perioperative treatment, because it has incalculable infectious and incompatibility risks.[147] Above that, it is expensive and suffers from insolvable logistical problems. Depending on the individual level of hemoglobin concentration, hemodilution improves blood rheology.[148] Therefore, hemodilution is not only a suitable alternative, but can be beneficial to the patient. Decreasing the hemoglobin value is, for example, what the circulation does during endurance training.[149] And this is the physiologic basis for preoperative normovolemic hemodilution to be applied to minimize the intraoperative transfusion rate.[150] Consequently, according to current knowledge, it is not inevitable to replace erythrocytes from the first milliliter of blood loss. Only a decrease below a certain hemoglobin value, individually depending on age, hemodynamic state, and previous illnesses, triggers a transfusion of concentrated erythrocytes.

Plasma components seem to be primarily dispensable as well. What might be correct for coagulation factors, however, has great impact when extended toward plasma proteins. According to the classic Starling concept, they must be maintained at a physiologic plasma concentration to preserve vascular barrier function.

Maintaining a physiologic state of the body fluid compartments as far as possible would mean a careful and adequate on-line substitution of actual fluid losses.

Interstitial Edema: The Price of Traditional Fluid Handling?

A conventional infusion regimen during major surgery is normally not based on physiologic facts but is predicated on, in doubt, liberal crystalloid handling. Application of artificial colloids is tolerated, but suspected to induce coagulation disorders, anaphylaxis, acute renal failure, and pruritus.[87,151] Human albumin is currently not considered a suitable alternative for acute volume replacement in most countries, mainly for financial reasons. Accordingly, some textbooks still recommend coping with acute bleeding by an infusion of crystalloids at threefold to fourfold the actual blood loss.[28] An assumed hypovolemic state after fasting and a strong belief in an exorbitant insensible perspiration due to major surgery,[13,152] together with a primarily fluid-consuming third space, leads to preoperative crystalloid loading (*e.g.*, 2 ml/kg per hour of fasting).[19] This is frequently followed by high basal crystalloid infusion rates of up to 15 $ml \cdot kg^{-1} \cdot h^{-1}$ as a perioperative standard measure at least for major intraabdominal surgery.[15,27] An increase in excretory kidney function from liberal crystalloid handling is expected and is an important argument to perform volume overload. From this point of view, fluid is only "offered" to the circulation and can easily be excreted if it falls into disuse. Also, a decreased circulatory state during induction of general or neuraxial anesthesia is widely spread treated or even anticipated with fluid loading. Despite often being diagnosed as merely a relative hypovolemia due to a decrease of sympathetic tone, an infusion of crystalloids or colloids is considered to be harmless in contrast to vasopressor application, which threatens organ function, mainly that of the kidneys.[153,154] Therefore, "clinicians are reluctant to use norepinephrine."[154]

The general aim to sufficiently substitute an assumed preoperative deficit and perioperative insensible losses (*i.e.*, insensible perspiration plus fluid shifting out of the circulation) still leads to positive sensible fluid balances (*i.e.*, blood loss and urinary output *vs.* infused fluids and blood products) of up to 10 l at the end of major abdominal surgery.[16,155–158] A related perioperative body weight gain at approximately the same extent[16,155–159] indicates, however, that the contribution of the insensible perspiration to perioperative fluid needs should be small. And indeed, as early as in 1977, Lamke *et al.*[152] performed direct measurements using a specially designed humidity chamber and clearly showed the insensible perspiration to be generally highly overestimated. The basal evaporation of approximately 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$ in the awake adult increases to, at the most, 1 $ml \cdot kg^{-1} \cdot h^{-1}$ during large abdominal surgery including maximal bowel exposure. Moreover, the impact of preoperative fasting on preoperative volume state is negligible: Even after an extended fasting period without concomitant bowel preparation, intravascular blood volume seems to be within normal ranges.[60] Anyway, the current fasting guidelines have more and more decreased the recommended preoperative period of no oral intake, at least for clear liquids,[58,59] and bowel preparation is currently being severely questioned.[56,57] Also, treatment of relative hypovolemia with volume instead of vasopressors, despite being in part successful if blood pressure is the only target,[160,161] highly impacts the integrity of the body fluid compartments.

Intended volume expansion before induction of anesthesia *via* preoperative volume loading, despite still being widely performed, is at least questionable, because it accepts collateral damage: Crystalloids are physiologically distributed within the whole extracellular compartment, *i.e.*, as mentioned above, four fifths must leave the vasculature. This is illustrated by figure 4, indicating that the perioperatively infused amount of crystalloids corresponds to the perioperative weight gain. But also, isooncotic colloids do not completely remain within the circulatory compartment under such conditions as generally expected. Rather, to approximately 60% they do not expand blood volume but directly load the interstitial space.[13,33] Infusing fluid not *before* but *when* relative hypovolemia occurs seems at first to be more reasonable, because volume effects of colloids have been demonstrated to be context sensitive.[13] The volume effect is defined as that part of an infused bolus that does not shift outward but remains inside the vascula-

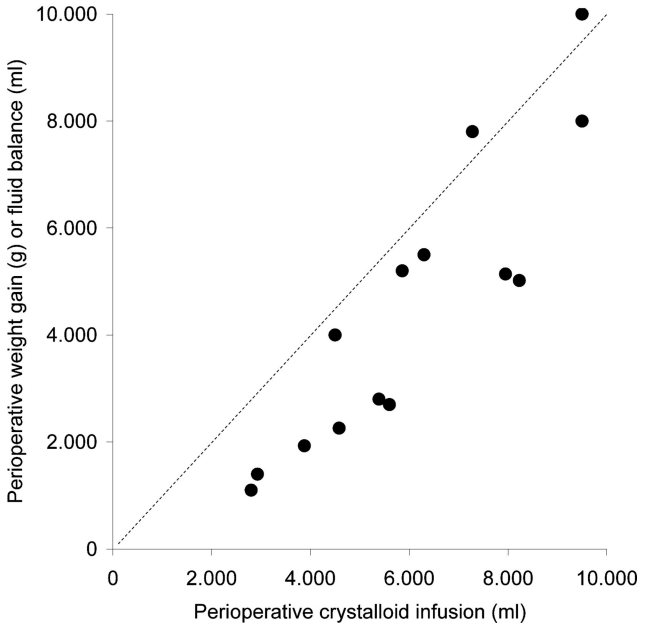

Fig. 4. Fifteen exemplary study groups suggest that perioperative weight gain increases with the perioperative amount of infused crystalloids.[8,11,16,17,44,45,155–158,198] This illustrative diagram does not consider the number of patients in each study, only contains mean values without SD, and ignores intraoperative blood loss and insensible perspiration, as not reported in all studies. *Dashed line* = line of equality.

ture.[31–33] A simultaneous infusion of iso-oncotic colloids during acute bleeding, *i.e.*, when carefully maintaining intravascular normovolemia, led to volume effects of more than 90%.[32,34] In contrast, approximately two thirds of an additional bolus of the same preparations in a normovolemic patient leaves the vasculature toward the interstitial space within minutes (fig. 5).[33] Consequently, volume effects of colloids depend on the "context," *i.e.*, the volume and hydration state of the patient.[13] Above that, treating vasodilation with colloids ignores the fact that the cause of the intravascular volume expansion, an indirect vasodilatory effect of anesthetics, must be expected to terminate, *i.e.*, the vascular tone will be restored, at the end of surgery. Relative hypervolemia follows and occasionally causes postoperative pulmonary edema.[145] The kidney is not of much help in this situation: Because of significant surgical stress, the human body actively decreases excretory kidney function,[9,162,163] obviously and reasonably to protect its fluid compartments.

Nevertheless, blood volume normally remains at preoperative levels even under generous fluid handling.[31,32,164] This is in accord with a recently published mathematical description of perioperative fluid shifting during abdominal surgery. According to this model, intravenously applied crystalloids exceeding a certain level shift completely out of the circulation, loading the interstitial space.[164] This phenomenon is illustrated by the clinical observation that "prophylactic" crystalloid boluses in normovolemic patients have been shown to have no major effect on the incidence or severity of anesthesia-related hypotension in obstetric patients.[165–168]

Consequently, interstitial edema is clearly the price for maintaining intravascular volume according to traditional recommendations, treating deficits that, in fact, do not exist with inadequate preparations. Colloids and crystalloids cannot be exchanged by simply adapting the amount. Actual losses from the vasculature are often treated by loading the entire extracellular compartment with crystalloids. But also the use of colloids does not always follow a rational concept.

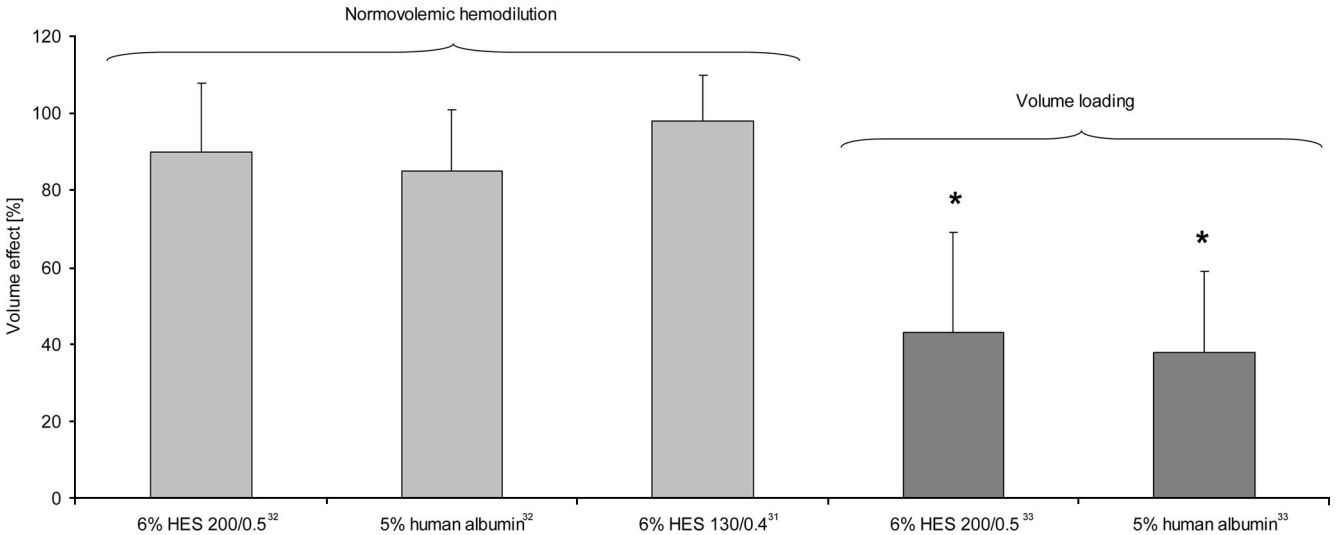

Fig. 5. The context sensitivity of volume effects of iso-oncotic colloids (the volume effect is that part of the colloid that remains within the circulation and does not primarily shift outward). As a substitute during acute bleeding, carefully maintaining normovolemia throughout the procedure, 6% hydroxyethyl starch (HES) 200/0.5, 5% human albumin, and 6% HES 130/0.4 (*left columns*) had volume effects of more than 90%. Volume loading of the normovolemic, by contrast, led to volume effects of 6% HES 200/0:5 and 5% human albumin (*right columns*) of approximately 40%. Blood volumes were assessed before and after intervention *via* double-label technique.[31–33] n = 10 each. Values are mean ± SD. * $P < 0.05$ *versus* normovolemic hemodilution.

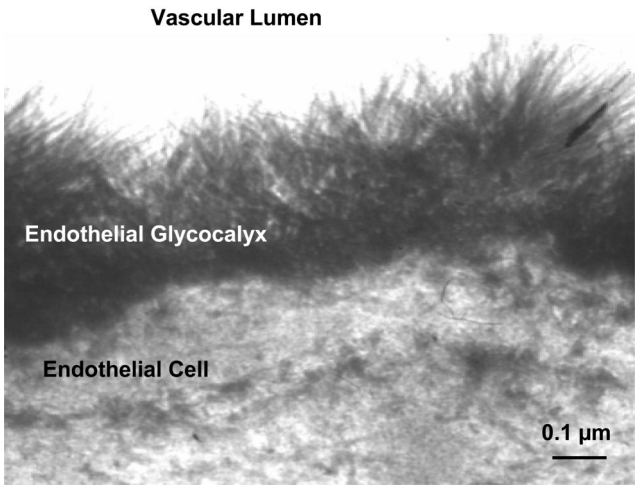

Fig. 6. Electron microscopic view of the endothelial glycocalyx. Staining of the glycocalyx was performed in modification of a method described by Vogel *et al.*,[177] based on an *in situ* stabilization of the glycocalyx by intracoronary application of a fixative containing lanthanum and glutaraldehyde.[170,173]

The Shifts toward the Interstitial Space: The Beauty and the Beast

Fluid shifting toward the interstitial space can systematically be divided into two types: Type 1, the physiologic shift, occurs principally all the time. It represents an almost colloid-free shift of fluid and electrolytes out of the vasculature, occasionally at a pathologic amount, *e.g.*, if large amounts of isotonic crystalloids are infused. This type of fluid shift occurs even if the vascular barrier is intact. Type 2, the pathologic shift, consists of fluids containing protein close to plasma concentration, crossing a functionally altered vascular barrier. The latter occurs inconstantly and is perioperatively related to the type, extent, and duration of surgery.[105] It is the result of two iatrogenic problems: first, a surgical one, increasing the protein permeability of capillaries and venules by up to eight times by endothelial damage due to mechanical stress, endotoxin exposure, ischemia–reperfusion injury, or inflammation[169]; and second, an anesthesiologic one, having the power to in addition cause an impressive pathologic shift of protein and fluid toward the tissue in the context of acute hypervolemia.[33] The mechanism behind both phenomena seems to be an alteration of the endothelial glycocalyx.

The Endothelial Glycocalyx: The Gateway to the Interstitial Space

A healthy vascular endothelium is coated by the endothelial glycocalyx (fig. 6).[170–173] This structure is a layer of membrane-bound proteoglycans and glycoproteins and was primarily regarded to have a thickness of only tens of nanometers.[174] Meanwhile, an endothelial surface layer, consisting of the endothelial glycocalyx and bound plasma proteins and fluids, with a functional thickness of more than 1 μm has been identified.[173,175–177] This layer, together with the endothelial cells, is part of the double-barrier concept of vascular permeability, identifying the glycocalyx as a second competent barrier in addition to the endothelial cell line opposing to unlimited extravasation.[173] By exerting a vital role on the physiologic endothelial permeability barrier[176,178] and preventing leukocyte and platelet adhesion,[179] it mitigates inflammation and tissue edema.[170–172]

The amount of plasma fixed within the endothelial surface layer and, therefore, quantitatively not participating in the normal blood circulation is approximately 700–1,000 ml in humans.[32,172,180] However, this noncirculating part of plasma volume is in a dynamic equilibrium with the circulating part.[171] Recently, it has been shown experimentally that a certain, fortunately small, minimal plasma concentration of albumin could represent a basic premise of the functional integrity of the endothelial surface layer.[176,181]

The Starling Principle Meets the Endothelial Glycocalyx

The prerequisite for the classic Starling principle to be able to bind water within the vascular system is a significant colloid osmotic pressure gradient between the intravascular and extravascular space. However, several experiments have shown that this equation cannot be correct.[182,183] The expected lymph flow, based on calculations according to the Starling principle, does not equal the measured flow.[184] Even after equilibration of intravascular and extravascular oncotic pressure in the isolated single microvessel model, the vascular barrier function remains intact.[178] There seems to be an oncotic gradient directly across the endothelial surface layer that defines vascular integrity, so that the presence of this layer should be the basic requirement for a physiologic barrier function.[176] In a rat mesenteric microvessel model, the effective colloid osmotic pressure difference opposing filtration was near 70% of the luminal osmotic pressure, though the colloid concentration outside equalled that inside the lumen of the microvessel.[178] It was proposed that the endothelial glycocalyx acts as a primary molecular filter and generates the effective oncotic gradient within a very small space.[182,183,185] Transcapillary fluid exchange seems not to depend on the global difference between hydrostatic and oncotic pressure between blood and tissue. Rather, the hydrostatic and oncotic pressures between the blood and the small space directly underneath the endothelial glycocalyx, but still inside the anatomical lumen of the vessel, are decisive here (fig. 7).[176,182,183] Taking the endothelial

surface layer into consideration, the Starling equation needs to be modified from its traditional form into:

$$J_v = K_f([P_c - P_i] - \sigma[\pi_{esl} - \pi_b]),$$

where J_v = net filtration; K_f = filtration coefficient; P_c = capillary hydrostatic pressure; P_i = interstitial hydrostatic pressure; σ = refection coefficient; π_{esl} = oncotic pressure within the endothelial surface layer; and π_b = oncotic pressure beneath the endothelial surface layer.

All this indicates a dependency between an alteration of the endothelial surface layer and protein or colloid shifting toward the interstitial space. Destruction of the endothelial surface layer and, therefore, the vascular barrier, leads back to the conditions proposed by the classic Starling equation, entailing transcapillary fluid shifting to equalize hydrostatic and oncotic pressures between tissue and blood—a catastrophe, if the interstitial colloid osmotic pressure equals that of the plasma.

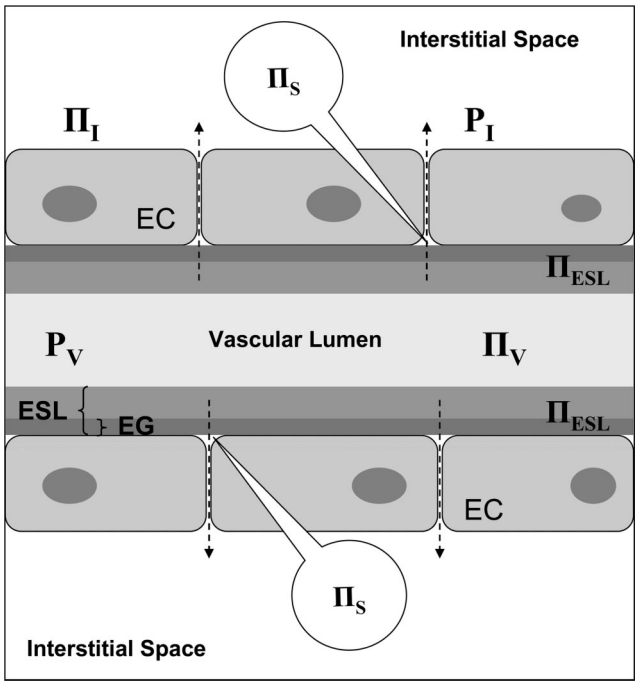

Fig. 7. The "revised" Starling principle.[176,178] The hydrostatic pressure in the vascular lumen (P_V), which largely exceeds the interstitial pressure (P_I), forces fluid outward. The endothelial glycocalyx (EG) binds plasma proteins, forming the endothelial surface layer (ESL) with a high internal oncotic pressure. The low net flux passing through the EG (*arrows*) has a sparse protein concentration; the oncotic pressure underneath the EG is low. Accordingly, an inward-directed oncotic pressure gradient develops just across the EG, while the proteins in the small space underneath the EG are continuously cleared toward the interstitial space *via* the remaining net flux. The extremely simplified illustration does not consider the venular site of the revised model, suggesting free and easy access of plasma proteins toward the interstitial space.[176] Because the hydrostatic force is low there, this should be no problem. Π_{ESL} = oncotic pressure within the endothelial surface layer; Π_I = oncotic pressure in the interstitial space; Π_S = oncotic pressure below the endothelial glycocalyx (subglyceal); Π_V = oncotic pressure in the vascular lumen; EC = endothelial cell.

This implies that, perioperatively, the endothelial glycocalyx should be preserved to inhibit a pathologic type 2 fluid shift into the interstitium. But how can this be achieved clinically?

Perioperative Protection of the Endothelial Surface Layer

Diminution of the endothelial glycocalyx leads to platelet aggregation,[179] leukocyte adhesion,[186] and an increase in endothelial permeability, causing tissue edema.[170,176] According to experimental studies, ischemia–reperfusion,[170,173] proteases,[187] tumor necrosis factor α,[188] oxidized low-density lipoprotein,[179] and atrial natriuretic peptide[175] have the power to degrade the endothelial glycocalyx. While surgical stress itself is well known to cause release of several inflammatory mediators,[9,162,163] atrial natriuretic peptide release is triggered by iatrogenic acute hypervolemia.[189–192] This is in accord with the observation that intravascularly applied boluses of colloid increased the plasma protein filtration from the vascular bed in cardiopulmonary-healthy human subjects.[33] Obviously, despite not being easy to achieve, maintaining intravascular normovolemia could be the key in the hands of the anesthesiologist to protect the endothelial glycocalyx beyond the hardly avoidable damage caused by inflammatory mediators due to trauma and surgery. This could minimize pathologic fluid and protein shifts toward the interstitium *via* preservation of the endothelial glycocalyx. Above that, a certain minimal plasma protein content should be inevitable to form the endothelial surface layer *in vivo*.[176,181]

Crystalloid *versus* Colloid: Time to End an Erroneous Discussion

Recent comparisons of patient outcome after resuscitation using either crystalloids or colloids, irrespective of the actual reason of a decreased circulatory state,[87,91,92] illustrate in an excellent manner what the so-called crystalloid *versus* colloid discussion[1–3] suffers from: Infusion solutions are generally not considered to be what they really are: drugs with indications, contraindications, and side effects. Ringer's solution as the only applied type of fluid during major abdominal surgery in humans decreased the mean tissue oxygen tension in the deltoid muscle for 24 h postoperatively by 23%, whereas additional treatment with hydroxyethyl starch led to a mean increase of 59%.[18] Obviously, a considerable difference in interstitial architecture results from using colloids instead of crystalloids for volume replacement, and this seems quite logical. As extensively described above, isotonic crystalloids are distributed within the whole extracellular compartment, *i.e.*, four fifths leave the vasculature, whereas iso-oncotic colloids have been designed to remain within the circulatory space. Consequently, the primary indication of crystalloids is replacement of fluid losses *via* (1) insensible perspiration and (2) urinary

output. Colloids, by contrast, are indicated to replace plasma deficits due to (2) acute blood loss or (2) protein-rich fluid shifts toward the interstitial space (pathologic type 2 shift).[97] Despite its being recommended[28] and still being widely performed, there is no rationale to substitute the first 1,000 ml of blood loss with a threefold to fourfold dose of isotonic crystalloids. Nor is there evidence to increase crystalloid infusion rate when patients seem to be clinically hypovolemic during surgery, despite intact extracellular fluid balance. This must induce an impressive (physiologic type 1) shift toward the interstitial space. Therefore, not only the amount, but also the kind, of applied fluid is crucial for patient outcome. Consequently, we must use the right kind of fluid in appropriate amounts at the right time to reduce collateral damage. From this point of view, it is erroneous to compare two classes of drugs with different indications regarding their impact on patient outcome.[87,91,93,94] Rather, we must carefully distinguish between the different types of losses and treat them accordingly.

A discussion of this topic should, therefore, be focused on crystalloid *and* colloid—when to use what and at which amount, to minimize fluid shifting as far as possible.

Minimizing Type 1 Shifting (Crystalloid)

By using crystalloids as a substitute of acute blood losses, *i.e.*, infusing the entire extracellular space, interstitial edema is part of a questionable fluid concept and not a surprising accident. Accordingly, this type of fluid shifting should be minimized by using crystalloids only to replace urine production and insensible perspiration and by using iso-oncotic colloids for substitution of acute blood loss.

Minimizing Type 2 Shifting (Crystalloid and Protein)

To prevent this type of fluid shifting, it seems crucial to protect the endothelial surface layer. Perioperative alteration of this structure has two main causes: first, the release of inflammatory mediators due to surgical trauma; and second, the release of atrial natriuretic peptide during iatrogenic acute hypervolemia. Accordingly, some degree of interstitial edema seems to be unavoidable despite modification of perioperative fluid handling. The dimension of surgical stress–induced inflammation and vessel leakiness is proportional to the degree of injury.[193] The dimension of glycocalyx impairment has been shown to correspond to the surgical impact.[194] Even though a normal, well-controlled inflammatory response in a previously healthy patient almost always results in an uneventful recovery,[193] the resultant vessel leakiness seems to be inescapable. Nevertheless, an atraumatic surgical technique could be beneficial here. Anesthesiologists might contribute to a reduction of stress release of inflammatory mediators by using neuraxial blocks. The endocrine response to surgery consists of an increased secretion of catabolically active hormones, most importantly cortisol, glucagon, and catecholamines.[195,196] Single-dose neural blockade, applied as either intraoperative epidural or spinal anesthesia, has only a transient stress-reducing effect, without prolonged endocrine or metabolic effects.[196] Above that, epidural blockade is only partially effective in blocking the endocrine–metabolic responses after upper body procedures, because not everything is affected by epidural blockade.[195,197] Single-shot blocks such as spinal anesthesia cannot achieve a sufficient reduction of inflammatory mediators.[196] Therefore, continuous neuraxial analgesia over 48–72 h using local anesthetics seems to be a possibility to reduce the metabolic stress response.

Nevertheless, carefully maintaining intravascular volume without hypervolemic peaks as far as possible currently seems to be the most promising concept. Prophylactic fluid boluses to anticipate acute bleeding or to extend intravascular blood volume in a primary normovolemic patient should no longer be considered state-of-the-art.

The situation changes when the glycocalyx is deteriorated during inflammation, ischemia, sepsis, or hypervolemia. Theoretically, colloids are only partly reflected at the vascular barrier in this situation. Despite the fact that there are no scientific data supporting this, many anesthesiologists use crystalloids in this situation. But is it really justified to consider an intentional load of the interstitial space with crystalloids to be the best strategy? Or is it rather inadequate? The shift out of a leaky vasculature is protein rich, and causal treatment of the intravascular deficit means an infusion of colloid osmotic force. Despite that this would lead to a shift quantitatively comparable with that when infusing crystalloid if the vascular barrier were completely open (which should be a rare case), it should be tried. Achieving a restoration of the circulating blood volume by infusing colloids to maintain intravascular normovolemia would reduce the interstitial load even if there is only a rudimentary competence of the vascular barrier. A central question in this context is: Which colloid is inert when it enters the interstitial space at a high amount, and which is not? The interstitial albumin concentration, for example, does not seem to differ relevantly from that which can be found in plasma, even under normal conditions.[183] Therefore, this natural colloid is an option in septic patients. However, future scientific efforts should concentrate on the less expensive, artificial alternatives.

During major surgery, it is nearly impossible to maintain normovolemia without producing edema. However, the occurring intravascular hypovolemia due to a protein-rich type 2 shift toward the tissue should be treated causally, *i.e.*, with colloids. Using crystalloids in this

situation aggravates this pathologic by a physiologic type 1 shift, which further increases the interstitial load. There are no clinical data supporting such an approach and, from a theoretical standpoint, it might even worsen the problem.

A Rational Approach to Perioperative Fluid Management

The goal of perioperative fluid application is the same than that of the cardiovascular system under normal conditions: an adequate blood flow in vital and, as far as possible, in traumatized tissues, as not to compromise the first and to enable effective wound healing in the latter. The focus of our efforts should be to avoid collateral damages, *i.e.*, interstitial edema, as far as possible. Therefore, it might be helpful to change our way of thinking from fluid "therapy" toward fluid "substitution." Above that, it is only a half-truth to proclaim a more restrictive therapy to be superior to a liberal one. Rather, an adequate and timely replacement of actual losses with appropriate preparations seems to be an ideal primary approach. Therefore, we should divide fluid therapy into two components: (1) replacement of fluid losses from the body *via* insensible perspiration and urinary output and (2) replacement of plasma losses from the circulation due to fluid shifting or acute bleeding. While a "goal-directed" approach *via* circulatory surrogates is, in principle, possible to replace plasma losses, the extracellular compartment cannot currently be monitored. Therefore, losses from the latter should be replaced based on a protocol:

1. The extracellular deficit after usual fasting is low.[60]
2. The basal fluid loss *via* insensible perspiration is approximately 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$, extending to 1 $ml \cdot kg^{-1} \cdot h^{-1}$ during major abdominal surgery.[152]
3. A primarily fluid-consuming third space does not exist.

Plasma losses out of the circulation have to be replaced with iso-oncotic colloids, presuming the vascular barrier to be primarily intact and acknowledging that colloidal volume effects are context sensitive. The basis should be a timely replacement of visible blood losses, possibly supplemented by a goal-directed approach. Goals depend on local and individual circumstances and can vary from the maintenance of heart rate and blood pressure within a normal range in daily routine, up to stroke volume control *via* pulse pressure variation or esophageal Doppler in special cases. Importantly, despite being helpful, extended monitoring does not primarily seem to be the diagnostic hardware we urgently need to change in order to apply a more rational fluid concept. Rather, it seems warranted to replace the infusion of crystalloid by colloid if we detect the patient's circulation to be in need of additional volume.

Establishing a modern approach to perioperative fluid handling is currently hindered by the claim of successful studies to have treated their patients restrictively.[8,11,44,45] Until recently, this has led to skepticism among clinicians, because many believe that restrictive fluid handling means depriving patients of their actual needs, leading to dehydration, which must, logically, lead to a decreased circulatory state due to intravascular hypovolemia. A careful comparison of the applied study protocols to measured values of preoperative blood volume after overnight fasting and insensible perspiration, however, reveals that the fluid regimens were mostly not restrictive in the true sense of the word, but represented an adequate substitution of fluid needs. A measurable weight gain even in restricted study groups[8,11] indicates that there is still room for improvements in this context. To tap the full potential will be an important challenge in the next years.

Conclusion

We believe that a classic third space does not exist. Crystalloid overload, as well as iatrogenic deterioration of the vascular permeability barrier, can induce impressive fluid and protein shifting toward the interstitium. Consequently, and in accord with clinical studies, preoperative volume loading in normovolemic patients and routine replacement of high insensible and third space losses should be abolished in favor of demand-related fluid regimens. Fluid restriction in successful clinical outcome studies was not restrictive, but strongly related to the patient's actual losses. An adequate replacement of fluid needs seems to have the power to improve patient outcome and should be considered the therapy of choice to minimize perioperative fluid shifting.

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