Best Practice & Research Clinical Anaesthesiology 23 (2009) 145–157

Contents lists available at ScienceDirect

Best Practice & Research Clinical Anaesthesiology

journal homepage: www.elsevier.com/locate/bean

1

The 'third space' – fact or fiction?

Matthias Jacob, MD, Staff Anesthesiologist [1,*], Daniel Chappell, MD, Staff Anesthesiologist [1], Markus Rehm, MD, Associate Professor

Clinic of Anaesthesiology, Ludwig-Maximilians-Universitaet Muenchen, Nussbaumstrasse 20, 80336 Munich, Germany

Keywords:
third space
endothelial glycocalyx
endothelial surface layer
vascular permeability
fluid management

For decades, the 'third space' was looked upon as an actively consuming compartment. Therefore, perioperative fluid regimens were traditionally based on a generous replacement of this assumed primary loss, in addition to deficits due to insensible perspiration and fasting. The practical consequence was an extremely positive fluid balance in order to maintain blood volume during major surgery. Whereas the insensible perspiration and the preoperative deficits are in fact often negligible, and the third space appears to be only a fictional construct, the excess fluid most likely accumulates interstitially. Such shifting is related to a destruction of the endothelial glycocalyx, a key structure of the vascular barrier, by traumatic inflammation and iatrogenic hypervolaemia. This explains why patients undergoing major surgical interventions benefit significantly from an infusion regimen which does not substitute but avoids 'third-space shifting'. In summary, eradicating this notion from our minds could be a further key to achieving perioperative fluid optimisation.

Perioperative fluid management and vascular physiology are currently in the focus of medical research[1–9], and fundamental changes in our views on these issues are continuing.[3,4,7] This is surprising, as for a long time quantitative fluid management has been neglected in the perioperative discussion in favour of the debate on colloids versus crystalloids[10,11] and proposals for the ideal composition of saline fluids.[12] During recent years, however, the main focus has increasingly been on the quantity of applied fluids in general.[5,6,13–21] Until very recently, a traditional view dominated this discussion: due to an assumed intravascular deficit after fasting[22], preoperative volume loading is still

* Corresponding author. Tel.: +49 89 5160 2691; Fax: +49 89 5160 4446.
E-mail address: matthias.jacob@med.uni-muenchen.de (M. Jacob).
[1] Both authors equally contributed to this work.

1521-6896/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bpa.2009.05.001

considered indispensable by many.[16,20,23,24] Moreover, a strong belief in an insensible perspiration increasing exponentially with damage to the skin barrier[25], as well as an inevitable and impressive fluid shift into a primarily consuming 'third space', led to an aggressive perioperative fluid approach by generations of anaesthesiologists.[26] An accompanying accumulation of fluid in tissues was interpreted as an unavoidable collateral damage.[27,28]

However, is the 'third space' really the root of all evil concerning pathological fluid shifting, or is this compartment nothing more than a fictional fairy tale? Or does the truth lie somewhere in between?

In this article we illuminate this mystery from a primarily physiological standpoint, and further combine these basics with clinical research results and current insights concerning the vascular barrier.

Fluid shifting: trigger or effect of traditional infusion behaviour?

Fluid shifting is an often recognised phenomenon during and after surgical procedures. However, it is still unclear whether surgery and trauma cause the main part of an impressive primary fluid shift outwards, which must be treated with large amounts of fluid, or whether an overwhelming infusion therapy causes severe perioperative problems which should be avoidable. In fact, traditional fluid handling during major surgery in humans has been shown to cause an excess of several litres in the perioperative fluid balance[3,7,29,30], that is, measurable input (infusions and transfusions) minus measurable output (blood loss and urine production). This was traditionally interpreted as successful perioperative treatment of three different kinds of losses, which are unmeasurable in clinical routine: the preoperative deficit, insensible perspiration and an inevitable 'third-space' shift caused by surgery and trauma.[31] A related perioperative body weight gain of up to 10 kg[17,31–35], however, indicates that somewhere along the line something is going wrong. Indeed, as early as in 1977, Lamke and co-workers performed direct perspiration measurements using a specially designed humidity chamber and clearly showed the insensible perspiration to be generally highly overestimated.[36] The basal evaporation of about 0.5 ml kg^{-1} h^{-1} through the skin and airway in the awake adult increased to, at the most, 1 ml kg^{-1} h^{-1} during major abdominal surgery, including losses through the surgical wound due to maximal bowel exposure, substantiating the idea that the contribution of insensible perspiration to perioperative fluid needs should be small. Moreover, the impact of fasting on intravascular volume is limited; even after 10 h of fasting, intravascular blood volume appears to be within the normal range, at least in patients not receiving preoperative bowel preparation.[37] Furthermore, the recommended preoperative period of stopped oral intake of clear liquids is decreasing more and more in current fasting guidelines.[38]

Obviously, in the normal adult, our traditional fluid regimen largely exceeds the patient's losses due to preoperative deficit and insensible perspiration. The fact that blood volume is normally at preoperative levels after the surgical procedure[3,7,29,39,40] indicates that the fluid excess largely represents perioperative fluid shifting. For the traditionalists, this was a good explanation that their strategy of generously replacing these impressive losses, presumably towards a 'third space', should be right, but was this simple conclusion really correct? More than 20 years ago, Chan et al. provided an interesting experimental set-up which indicated that maybe not everything is what it seems to be.[41] They demonstrated in a rabbit model that surgical manipulation itself can cause a significant increase of 5–10% in the interstitial water load, without any infusion therapy during enteral anastomosis. An additional crystalloid infusion of 5 ml kg^{-1} h^{-1} doubled this oedema.

However, what is the role of the 'third-space' shift in this oedema-formatting process, obviously related to surgery and intravenous fluid application?

Fluid compartments of the human body

In humans, approximately 60% of the total body mass is water. In contrast to protozoa, which are surrounded by the primal ocean, the body cells of humans are not in direct contact with their nutrient solution. Evolution developed the human body as a complex system, integrating single cells into organ structures. The extra-cellular space, therefore, is now inside the body. To enable nutrition of the cells despite this deprivation, the extra-cellular space is functionally divided into the interstitial space, imitating the nutrient solution of protozoa, and the intravascular space. The latter is specialised for

a convective transport of oxygen and nutrient elements from the body surface – that is, the lung and the gastrointestinal system – to the direct surroundings of the cells. This enables their supply with nutrients and disposal of waste products and carbon dioxide.

Intracellular fluid comprises two-thirds of the body water. The remaining one-third – about 15 l in the normal weighted adult – comprises the extra-cellular volume (ECV, namely 20% of the total body mass) consisting of the plasma (about 3 l), the interstitial space (about 12 l) and small amounts of the so-called trans-cellular fluids[42,43] such as gastrointestinal secretions, cerebrospinal fluid and ocular fluid (Fig. 1). The latter are considered to be anatomically separated and not in dynamic equilibrium with the interstitial space and the plasma, in which water and small solutes can easily be exchanged.[43,44] The 'third space', nothing more than a perception so far, has functionally been allocated to this trans-cellular compartment.

The 'third space': the theory behind the story

Previous works have systematically divided the third space into anatomical and non-anatomical parts.[41,45,46] Anatomical losses are considered to be pathological fluid accumulations within the interstitial space which, together with the plasma, forms the 'functional' extra-cellular volume (fECV). The physiological fluid shift between the intravascular and interstitial space is considered to contain only small amounts of protein and small molecules, limited by an intact vascular barrier.[47] As long as it is quantitatively managed by the lymphatic system, a physiological shift does not cause interstitial oedema.[48] An overload of the lymphatic system, for example, by high volumes of iatrogenic fluid, can principally be resolved contemporarily through redistribution and urinary output. Non-anatomical losses, by contrast, formally represent the classical third-space shift, a part of the extracellular space functionally and anatomically separating from the rest.[43,44,49] Therefore, these fluids are considered to now be part of the 'non-functional' extra-cellular volume (nfECV).[42,50] This separation is believed to be caused primarily by major surgical procedures or trauma. According to this traditional interpretation, fluid trapped within the classical third space is lost permanently for extra-cellular exchange. In order to nevertheless maintain the functional extra-cellular volume (fECV), the traditional perioperative fluid excess was considered an inevitable therapeutic reaction by generations of anaesthesiologists.[49] However, what are the underlying data?

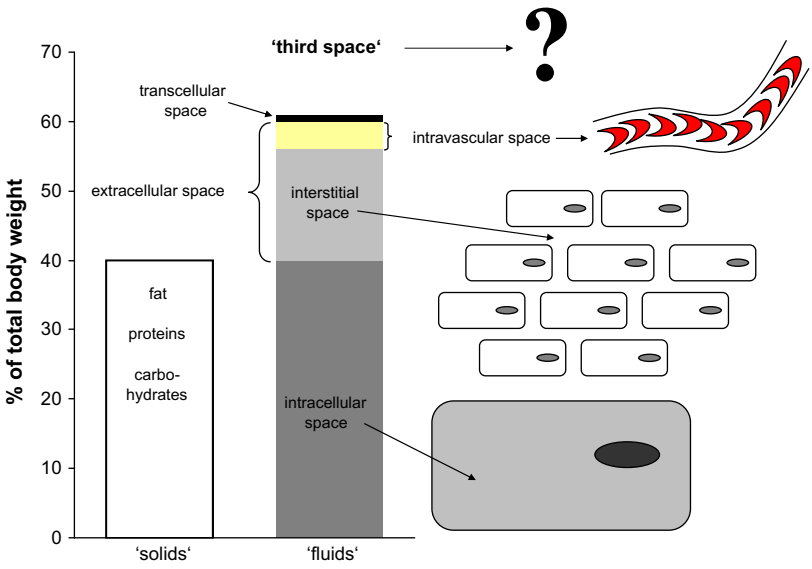

Fig. 1. Composition of the body compartments.

Third space: who seeks will find, or maybe not?

Classical third-space fluid losses have never been measured directly, and the actual location of the lost fluid remains unclear.[43] Neither the gut[51] nor traumatised tissue[52] contains these large amounts of fluid, and no other trans-cellular space has been shown to relevantly enlarge due to perioperative fluid shifting. Previous studies have merely 'quantified' these losses indirectly by measuring fECV before and after surgery through tracer-dilution techniques[43,46], presuming the total ECV to remain constant. Accordingly, the nfECV was calculated by subtracting the post-operative fECV from the preoperative one. Tracer-dilution techniques are based on the principle of applying a known amount of a suitable tracer into the scanned fluid compartment; the concentration of the tracer within this compartment after an adequate equilibration interval leads, through the amount of injected dye, to its distribution volume. A single sampling method depends on full equilibrium occurring just before sampling. As it often varies inter- and intra-individually, the equilibration interval of choice can only be assumed. Therefore, single measurements are in severe danger of producing inaccurate results. In contrast, multiple sampling ensures that equilibration is actually obtained in each individual, provided that the sampling period is sufficiently long. Accordingly, continued multiple samples are recommended to calculate tracer spaces until equilibration is shown in each individual case.[46,53] Tracer-dilution methods are generally limited by three main questions which identify the three major shortcomings of their application to fECV measurements: (1) What is a suitable tracer, distributing evenly and exclusively within the fECV? (2) What is a suitable equilibration interval, allowing complete distribution but not interfering with redistribution or tracer elimination kinetics? Finally, (3) how can a method to quantify the fECV be reliably validated?

Despite serious concerns, various tracers, techniques, sampling times and mathematical calculations of the fECV have been used in past studies.[46] Not surprisingly, this has led to different results, and various conclusions have been drawn.

The two most common radioactive tracers were sulphate ($^{35}SO_4^{2-}$) and bromide ($^{82}Br^-$) ions. Adequate equilibration times to measure fECV have been reported to be up to 3 h for the sulphate[54] and over 10 h for the bromide tracer.[55] The limitations of these tracers are that bromide enters red blood cells and is excreted in bile[56], whereas sulphate is bound to plasma components[57] and accumulates in the liver, in the kidneys or during shock in muscular tissue.[54,58] For both tracers, the necessary time to achieve equilibration has been shown to be prolonged after surgery[49,50], haemorrhagic hypotension[49,59–61] or fluid overload.[62] Moreover, an important prerequisite for using tracer kinetics for volume measurements is a steady-state condition, which is hardly given during shock or surgery.[46,51,53,63] Therefore, an apparent increase in fECV should be common when using this approach in the perioperative set-up.

Those studies claiming to have found the famous third-space loss during surgery or haemorrhagic hypotension used the sulphate tracer in combination with either a single blood sample or very few samples, obtaining the measurements after 20–30 min of equilibration.[63–66] Although this may be adequate during normovolaemia and steady-state conditions, a prolonged equilibration time during haemorrhagic hypotension or surgery, leading to an incorrect high concentration of tracer in the plasma, may explain the apparently contracted fECV.[49,59,67]

Surprisingly, trials measuring the fECV using multiple blood samples after longer equilibration times found the opposite of the existing 'common knowledge', that is, an unchanged or even increased fECV.[49,51,55,59,63,67–77] Trials using the bromide tracer found this expansion of fECV after surgery, not accounted for by the calculated fluid balance.[55,59,68,69,72,73] Accordingly, and in contrast to the common assumption, most of the data do not support the existence of a third space.

Third space: fact or fiction?

The third space in its traditional interpretation is a functionally separated part of the extra-cellular compartment which cannot be localised, but primarily consumes fluid in the perioperative context. It is currently no more than a myth to explain the otherwise apparently unexplainable perioperative fluid shifting. The second view suggests abolishing this mystery and sticking to the given facts: fluid is

perioperatively shifted within the functional extra-cellular compartment, from the intravascular towards the interstitial space.

Perioperative fluid shifting towards the interstitial space is fact, whereas the classical third space is fiction.

The importance of this modern interpretation of perioperative fluid shifting lies in the cognition of the fact that we cannot simply tick off the fluid losses out of the circulation after having replaced them. Rather, the resulting interstitial oedema is a relevant and increasingly acknowledged clinical problem, endangering patient outcome. Its incidence seems to be related to perioperative fluid behaviour.

Fluid therapy: standard or liberal or restrictive or what?

Limited protocol-based perioperative fluid strategies might reduce the incidence of complications after major abdominal surgery.[3,13,14,28] In a multicentre study, Brigitte Brandstrup and co-workers investigated 141 patients undergoing major colorectal surgery.[13] They demonstrated that perioperative intravenous fluid restriction (mean 2740 vs. 5388 ml) significantly reduced the incidence of major and minor complications, such as anastomotic leakage, pulmonary oedema, pneumonia and wound infection. Nisanevic and colleagues found decreased postoperative morbidity, including a shortened hospital stay, under a protocol-based, more restrictive fluid therapy (1.2 l vs. 3.7 l). Their cohort was more heterogeneous, consisting of 152 patients scheduled for mixed abdominal surgery.[14] Holte and Kehlet recently recommended avoiding fluid overload in major surgical procedures as a conclusion of a systematic review of 80 randomised clinical trials.[5]

Conversely, various studies on minor interventions have suggested that patients benefit from a more liberal fluid application. Maharaj et al. have claimed large fluid amounts (1799 ± 53 vs. 212 ± 6 ml) during laparoscopic surgery to decrease pain and postoperative nausea and vomiting (PONV) in patients at high PONV risk.[20] Magner and co-workers found comparable effects, having infused 1900 ml within a mean procedure duration of 19 min.[78] Holte et al., however, relativised these results by demonstrating that the apparent beneficial effects after such an aggressive approach are related to a decreased coagulation state and a postoperative weight gain, which still existed 72 h after surgery.[79] During laparoscopy, however, they also found a liberal fluid handling (40 vs. 15 ml kg^{-1}) to decrease PONV and to improve postoperative lung function.[11]

Liberal perioperative fluid replacement shortens recovery time after minor surgery, whereas a loss-adapted approach may be beneficial during large interventions, reducing the incidence of vital complications.

However, what is the underlying mechanism? Why does the vascular barrier primarily function well in the normal adult but occasionally seem to fail? Why is the impact of fluid therapy obviously related to the extent of the surgical trauma?

A classical view of the vascular barrier

Large molecules and proteins cannot cross the intact vascular barrier in relevant amounts.[80] This enables the circulation to generate a positive intravascular blood pressure without unlimited fluid loss towards the interstitial space. Ernest Starling introduced his physiological model of the vascular barrier as early as in 1896: inside the vessels, the hydrostatic pressure as well as the colloid osmotic pressure are high.[81] In contrast, Starling postulated that the interstitial space not only contains a small amount of proteins but also has a low hydrostatic pressure. This theoretically results in a low net filtration rate per unit of time (Fig. 2). Consequently, a sufficient colloid osmotic pressure within the circulatory space is necessary to provide a physiologically active inward-directed force in order to successfully oppose the hydrostatic pressure gradient. According to this model, infused iso-oncotic colloids do not change the intravascular colloid osmotic pressure and cannot cross the barrier. Therefore, they should remain theoretically by 100% within the circulatory space. Infused crystalloids are free of colloid osmotic force and are therefore not retained at the vascular wall. Accordingly, they distribute within the whole extra-cellular – that is, the vascular (one-fifth) and the interstitial (four-fifths) – space for physiological reasons. This explains the clinical observation that prophylactic crystalloid boluses in the normovolaemic patient have been shown to have no major effect on the incidence or severity of anaesthesia-related hypotension.[82–85]

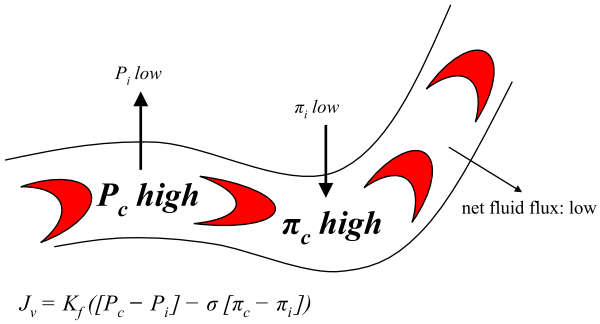

Fig. 2. The 'classical' Starling principle of vascular barrier functioning in arterioles and capillaries: an inward-directed colloid-osmotic pressure gradient is opposed to an outward-directed hydrostatic pressure of fluid and colloids. The thick arrows symbolize the two schematically opposing forces across the vascular wall, the small one the small net fluid filtration outwards 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. J_v, net filtration; K_f, filtration coefficient; P_c, capillary hydrostatic pressure; Π_i, oncotic pressure in the interstitial space; P_i, hydrostatic pressure in the interstitial space; Π_c, oncotic pressure in the vascular lumen; P_c, hydrostatic pressure in the vascular lumen; σ, reflection coefficient.

Therefore, crystalloid infusion increases the interstitial hydrostatic pressure and stresses the lymphatic system. Reabsorption and return of the fluid to the circulation through the lymphatic system are also impaired by surgery-induced inflammation.[86] As both conditions are common during major surgery under traditional fluid management, interstitial fluid accumulation should be common in this context.

According to Starling's theoretical model, infused iso-oncotic colloids remain within the circulatory space, whereas crystalloids primarily distribute within the whole extra-cellular space, even if the vascular barrier is intact.

The context sensitivity of colloidal volume effects

Direct blood-volume measurements have revealed that the presumed volume effect of about 100% for iso-oncotic colloids[87] exists only during normovolaemic haemodilution, that is, extracting blood and simultaneously replacing it with equal amounts of colloidal fluids. The volume effect is defined as that part of an infused bolus that does not shift outwards, but remains inside the vasculature.[29,30,39] During volume loading, that is, infusion of colloids to a primarily normovolaemic circulation without simultaneous blood withdrawal, they do not completely remain within the circulatory compartment at all. Rather, about 60% of the infused amount directly loads the interstitial space (Fig. 3).[6,30] This context sensitivity of the volume effect indicates that it might be more reasonable to infuse fluid not 'before' but

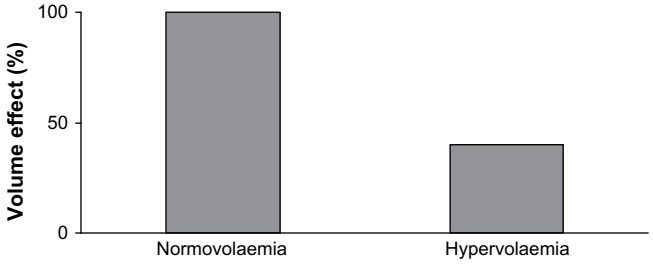

Fig. 3. The context sensitivity of volume effects of iso-oncotic colloids: while 6% hydroxethylstarch or 5% human albumin remain within the circulation to almost 100% if infused as a substitute during acute blood loss (left-hand column)[29], the preparations vanish out of the vasculature to a large extent if applied as a hypervolaemic bolus (right-hand column).[30] Drawn schematically according to Jacob et al (2007, *Lancet* **369:** 1984–1986) with permission.

when hypovolaemia occurs[6], because pharmacodynamics of colloids depend on the volume and hydration state of the patient before application.[6] In addition, the common practice of loading the patient before performing a neuraxial anaesthesia[83–85] is severely questionable in light of this fact: volume effects of iso-oncotic colloids are about 100% if used for substituting acute blood losses. Infusions resulting in hypervolaemia cause a tremendous shift of fluid and colloids towards the interstitial space.

However, what is the underlying pathomechanism by which hypervolaemia has the power to impair the functioning of a primarily intact vascular barrier? For the answer, we have to extend our view on vascular physiology towards a small structure which has been overlooked during the last decades.

The endothelial glycocalyx

Every healthy vascular endothelium is coated on the luminal side by an endothelial glycocalyx.[9,88–90] These membrane-bound proteoglycans and glycoproteins, together with bound plasma constituents, build up to the physiologically active endothelial surface layer with a functional thickness of over 1 μm.[90–93,108] It has been identified as having a major part in vascular barrier function[1,92] and in preventing leucocyte adhesion and platelet aggregation[94], mitigating inflammation and tissue oedema.[9,88,89] A non-circulating part of plasma volume – about 700–1000 ml in humans[9,29,95] – is fixed within the endothelial glycocalyx but in dynamic equilibrium with the circulating plasma.[89] Recent experiments have shown that a certain plasma concentration of albumin seems to be a basic premise for the functional integrity of this endothelial surface layer.[92,96]

Glycocalyx and Ernest Starling: a modern dream team

The theoretical prerequisite of Starling's principle to explain water retention within the vascular compartment is a significant inward-directed colloid osmotic pressure gradient between the intravascular and the interstitial space. Recent experiments have indicated that this classical principle might need an update. In a rat mesenteric microvessel model, the effective colloid osmotic pressure difference opposing filtration was nearly 70% of the luminal osmotic pressure, although the colloid concentration outside equalled that inside the lumen of the vessel.[1] Obviously, the interstitial protein concentration does not play the major role in this context. Rather, the endothelial glycocalyx appears to act as a molecular filter, actively retaining the plasma proteins hydrostatically forced outwards.[97–99] This increases the oncotic pressure within the glycocalyx[92], loading it to the functional endothelial surface layer, whereas the small space beneath, while still at the luminal side of the anatomical vessel wall, is practically protein free (Fig. 4).[92,97,98] Accordingly, and in clear contrast to the traditional assumption, transcapillary fluid loss actually seems to be limited by an oncotic pressure gradient across the endothelial glycocalyx, a structure that was unknown to Ernest Starling. Therefore, his classical principle needs to be updated, taking into consideration the current knowledge indicating a strong dependency of vascular integrity on the integrity of the endothelial glycocalyx. An intact endothelial glycocalyx is obviously a prerequisite of a functioning vascular barrier.

What dangers is the glycocalyx exposed to perioperatively, and what can we do to protect this shield?

Possible perioperative triggers for shedding of the endothelial glycocalyx

According to experimental studies, ischaemia/reperfusion[88,90], proteases[100], tumour necrosis factor-α[101], oxidised low-density lipoprotein[94] and atrial natriuretic peptide (ANP)[91] all have the power to degrade the endothelial glycocalyx.[4] Whereas surgical stress itself is well known to cause release of several inflammatory mediators[102,103], ANP release is triggered by iatrogenic acute hypervolaemia.[104,105] Obviously, avoiding intravascular hypervolaemia could be one key in the hands of the anaesthesiologist to protect the endothelial glycocalyx beyond a hardly avoidable basal damage due to trauma and surgery.

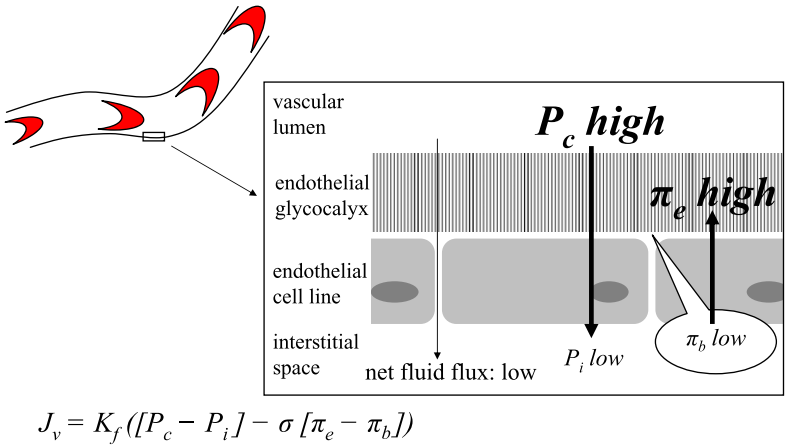

Fig. 4. The 'revised' Starling principle. The hydrostatic pressure in the vascular lumen (P_c), which largely exceeds the interstitial pressure (P_i), forces fluid outwards (left thick arrow). As it is loaded with plasma proteins, the endothelial glycocalyx has a high internal oncotic pressure (Π_e). The low net flux passing through the glycocalyx (small arrow) has a sparse protein concentration, and the oncotic pressure beneath the glycocalyx (Π_b) is low. Accordingly, an inward-directed oncotic pressure gradient (right thick arrow) develops just across the glycocalyx, while the proteins in the small space underneath the glycocalyx are continuously cleared towards 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 towards the interstitial space. As the hydrostatic force is low there, this should be no problem at all. J_v, net filtration; K_f, filtration coefficient; P_c, capillary hydrostatic pressure; Pi, interstitial hydrostatic pressure; σ, reflection coefficient; π_e, oncotic pressure within the endothelial glycocalyx; π_b, oncotic pressure beneath the endothelial glycocalyx.

Fluid shifting: a reinterpretation according to current concepts

Perioperative fluid shifting from the vasculature towards the interstitial space should currently be divided into two types.[3] Type 1 is a physiological, almost colloid-free shift of fluid and electrolytes out of the vasculature, which appears to happen to a small extent all the time. Nevertheless, it can rise to pathological amounts due to dilution of plasma proteins or an increased outward-directed hydrostatic pressure. The barrier itself, however, is not affected by this quantitative phenomenon, and the resulting clinical problem should be resolvable, in principle at least. Type 2, the pathological plasma shift, is protein-rich and therefore related to a morphological alteration of the vascular barrier. Since, most likely, it cannot be restored within a calculable period of time, this problem should be avoided as far as possible in the perioperative period.

Avoiding perioperative fluid shifting

Crystalloid versus colloid: a misleading discussion promotes type-1 shifting

The discussion on 'crystalloid versus colloid' has been going on for years.[10,11] It has led to comparisons of patient outcome after resuscitation using either crystalloids or colloids, ignoring the actual physiology behind a respectively decreased circulatory state.[106,107] This excellently illustrates the shortcoming of this discussion, actively negating the fact that infusion solutions are drugs with indications, contraindications and side effects.[3] The common recommendation to substitute the first 1000-ml blood loss with the three- to fourfold dose of isotonic crystalloids[26], or to just increase the crystalloid infusion rate when the patients appear to be clinically hypovolaemic during surgery, is a further outstanding example.

Acute bleeding primarily induces an isolated intravascular deficit. As colloid osmotic force is lost, a rational substitution below the transfusion border should be performed with iso-oncotic colloids, not

with crystalloids which distribute homogenously within the entire extra-cellular space, that is, four-fifths into the interstitial space.[22] Only one-fifth remains intravascular, which means that five times the amount of crystalloids would be required to achieve comparable intravenous effects, whereas a large part primarily loads the interstitial space, inevitably causing oedema. Consequently, using protein-free preparations to replace a loss of colloid osmotic force is not only unphysiological, but also most likely harmful.[22]

Extra-cellular protein-free losses caused by insensible perspiration and urine production are normally replaced through gastrointestinal resorption. This compensatory mechanism fails in the fasted patient and necessitates artificial replacement therapy with crystalloids, ideally in balanced form so as not to cause acid–base disorders.[106] Avoiding overinfusion of crystalloids should directly limit interstitial oedema. Therefore, crystalloids ought to be applied according to a careful calculation of actual extra-cellular losses.

Avoid hypervolaemia: the way to limit type-II shifting

Perioperatively, it appears to be crucial to protect the endothelial surface layer. Anaesthesiologists have only limited influence on the primary damage caused by the surgical trauma. A promising anaesthesiological concept might be avoidance of hypervolaemic colloidal peaks as far as possible in order to prevent ANP release. Intentional prophylactic volume-loading to extend intravascular blood volume prior to induction of anaesthesia or to anticipate acute bleeding might compromise the vascular barrier. Therefore, general application of such procedures should no longer be considered state of the art. Colloids should be infused when intravascular fluid losses (e.g., acute bleeding) occur, and not before. A causal therapy of vasodilation in the normovolaemic patient caused by general and/or neuraxial anaesthesia is, in principle, re-establishing vasotonus with a vasopressor in a moderate dose and not infusion of colloids. Mechanical ventilation can of course additionally reduce cardiac preload due to increased intrathoracic pressures. However, this effect is reversible within minutes when patients regain spontaneous breathing, in clear contrast to the impact of volume loading, inducing long-lasting and most likely harmful effects on body fluid compartments and the vascular barrier. Vasopressor therapy, applied alternatively in the normovolaemic patient in order to maintain cardiac preload by comprising the venous system, can easily be reduced when the iatrogenically induced haemodynamic alterations are terminated.

A modern discussion on perioperative fluid management should be focussed on a careful differential indication between crystalloids, colloids and vasopressors.

Conclusion

The classical ‘third space’ is most likely pure fiction. Rather, perioperative fluid shifting predominantly represents losses towards the interstitial space. At least in part, this is not inevitable, but caused by applying the wrong infusion solutions, with a false indication in an inadequate amount. A decided differential indication of balanced isotonic crystalloids and iso-oncotic colloids, in order to carefully maintain homeostasis of all fluid compartments, might be an important key to prevent perioperative fluid shifting. Crystalloids should be suitable to replace extra-cellular losses through insensible perspiration and urinary output. Colloids are the therapy of choice to replace acute blood losses below the transfusion border. As far as possible, hypervolaemia as well as hypovolaemia should be avoided at any time. This primary approach has to be re-evaluated permanently and, if necessary, modified according to individual requirements. If clinical signs of intravascular hypovolaemia occur, despite sufficient replacement therapy of measured and estimated losses, two explanations seem obvious: (1) blood loss has been underestimated, or (2) type-II shifting has been initiated. In both cases, intravascular application of further iso-oncotic colloid, not of crystalloid, should be considered.

All of these only apply to patients with a cardiocirculatory steady state. During acute bleeding in major trauma, or in patients suffering from systemic inflammatory response, the prevention of fluid shifting must certainly be set aside for an aggressive treatment of intravascular hypovolaemia.

Practice points

- The classical third space does not exist.
- Perioperative fluid shifting from the intravascular towards the interstitial space is a relevant pathogenetic factor to the patients.
- Fluid shifting can qualitatively be divided into physiological and pathological ones.
- Physiological type-I shift represents a protein-free shift across an intact vascular barrier, due to crystalloid hypervolaemia.
- Pathological type-II shift is protein-rich and is related to an alteration of the vascular barrier.
- Avoiding hypervolaemia protects the vascular barrier and minimises perioperative fluid shifting.

Research agenda

- Further procedure-specific research is warranted to evaluate the exact impact of rational quantitative fluid handling compared to traditional regimens.
- The impact of a requirement-adapted differential indication of colloids, crystalloids and vasopressors on patient outcome versus traditional fluid handling needs to be demonstrated.
- The benefit of a goal-directed approach, compared to a protocol-based one, to optimise the patient's volume state should be investigated.
- Fluid therapy guidelines considering current knowledge need to be established.

Conflict of interest

All authors declare to have no conflicts of interest.

Acknowledgements

This work was supported solely by institutional and departmental sources (Clinic of Anesthesiology, Ludwig-Maximilians University of Munich, Germany).

References

*1. Adamson RH, Lenz JF, Zhang X et al. Oncotic pressures opposing filtration across non-fenestrated rat microvessels. *The Journal of Physiology* 2004; **557:** 889–907.
2. Boldt J. Volume therapy in cardiac surgery: are Americans different from Europeans? *Journal of Cardiothoracic and Vascular Anesthesia* 2006; **20:** 98–105.
*3. Chappell D, Jacob M, Hofmann-Kiefer K et al. A rational approach to perioperative fluid therapy. *Anesthesiology* 2008; **109:** 723–740.
4. Chappell D, Jacob M, Becker BF et al. Expedition glycocalyx. A newly discovered 'Great Barrier Reef'. *Anaesthesist* 2008; **57:** 959–969.
5. Holte K & Kehlet H. Fluid therapy and surgical outcomes in elective surgery: a need for reassessment in fast-track surgery. *Journal of the American College of Surgeons* 2006; **202:** 971–989.
*6. Jacob M, Chappell D & Rehm M. Clinical update: perioperative fluid management. *Lancet* 2007; **369:** 1984–1986.
7. Jacob M, Chappell D, Hofmann-Kiefer K et al. Determinants of insensible fluid loss. Perspiration, protein shift and endothelial glycocalyx. *Anaesthesist* 2007; **56:** 747–764.
8. Joshi GP. Intraoperative fluid restriction improves outcome after major elective gastrointestinal surgery. *Anesthesia and Analgesia* 2005; **101:** 601–605.
9. Pries AR & Kuebler WM. Normal endothelium. *Handbook of Experimental Pharmacology* 2006; **1:** 1–40.
10. Bellomo R. Fluid resuscitation: colloids vs. crystalloids. *Blood Purification* 2000; **20:** 239–242.
11. Choi PT, Yip G, Quinonez LG & Cook DJ. Crystalloids vs. colloids in fluid resuscitation: a systematic review. *Critical Care Medicine* 1999; **27:** 200–210.
12. Dorje P, Adhikary G & Tempe DK. Avoiding latrogenic hyperchloremic acidosis – call for a new crystalloid fluid. *Anesthesiology* 2000; **92:** 625–626.

*13. Brandstrup B, Tonnesen H, Beier-Holgersen R et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Annals of Surgery* 2003; **238:** 641–648.
14. Nisanevich V, Felsenstein I, Almogy G et al. Effect of intraoperative fluid management on outcome after intraabdominal surgery. *Anesthesiology* 2005; **103:** 25–32.
15. Boldt J, Ducke M, Kumle B et al. Influence of different volume replacement strategies on inflammation and endothelial activation in the elderly undergoing major abdominal surgery. *Intensive Care Medicine* 2004; **30:** 416–422.
16. Campbell IT, Baxter JN, Tweedie IE et al. IV fluids during surgery. *British Journal of Anaesthesia* 1990; **65:** 726–729.
17. Dawidson IJ, Willms CD, Sandor ZF et al. Ringer's lactate with or without 3% dextran-60 as volume expanders during abdominal aortic surgery. *Critical Care Medicine* 1991; **19:** 36–42.
18. Holte K, Klarskov B, Christensen DS et al. Liberal versus restrictive fluid administration to improve recovery after laparoscopic cholecystectomy: a randomized, double-blind study. *Annals of Surgery* 2004; **240:** 892–899.
19. Lang K, Boldt J, Suttner S & Haisch G. Colloids versus crystalloids and tissue oxygen tension in patients undergoing major abdominal surgery. *Anesthesia and Analgesia* 2001; **93:** 405–409.
20. Maharaj CH, Kallam SR, Malik A et al. Preoperative intravenous fluid therapy decreases postoperative nausea and pain in high risk patients. *Anesthesia and Analgesia* 2005; **100:** 675–682.
21. Waters JH, Gottlieb A, Schoenwald P et al. Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. *Anesthesia and Analgesia* 2001; **93:** 817–822.
22. Holte K & Kehlet H. Compensatory fluid administration for preoperative dehydration – does it improve outcome? *Acta Anaesthesiologica Scandinavica* 2002; **46:** 1089–1093.
23. Coe AJ & Revanas B. Is crystalloid preloading useful in spinal anaesthesia in the elderly? *Anaesthesia* 1990; **45:** 241–243.
24. McCrae AF & Wildsmith JA. Prevention and treatment of hypotension during central neural block. *British Journal of Anaesthesia* 1993; **70:** 672–680.
25. Sear JW. Kidney dysfunction in the postoperative period. *British Journal of Anaesthesia* 2005; **95:** 20–32.
26. Kaye AD & Kucera AJ. Fluid and electrolyte physiology. In Miller RD (ed.). *Anesthesia*. Philadelphia: Churchill Livingston, 2005, pp. 1763–1798.
27. Haugen O, Farstad M, Kvalheim V et al. Elevated flow rate during cardiopulmonary bypass is associated with fluid accumulation. *The Journal of Thoracic and Cardiovascular Surgery* 2007; **134:** 587–593.
28. Lobo DN, Bostock KA, Neal KR et al. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. *Lancet* 2002; **359:** 1812–1818.
29. Rehm M, Orth V, Kreimeier U et al. Changes in intravascular volume during acute normovolemic hemodilution and intraoperative retransfusion in patients with radical hysterectomy. *Anesthesiology* 2000; **92:** 657–664.
*30. Rehm M, Haller M, Orth V et al. Changes in blood volume and hematocrit during acute preoperative volume loading with 5% albumin or 6% hetastarch solutions in patients before radical hysterectomy. *Anesthesiology* 2001; **95:** 849–856.
31. Shackford SR, Sise MJ, Fridlund PH et al. Hypertonic sodium lactate versus lactated ringer's solution for intravenous fluid therapy in operations on the abdominal aorta. *Surgery* 1983; **94:** 41–51.
32. Shackford SR, Fortlage DA, Peters RM et al. Serum osmolar and electrolyte changes associated with large infusions of hypertonic sodium lactate for intravascular volume expansion of patients undergoing aortic reconstruction. *Surgery Gynecology & Obstetrics* 1987; **164:** 127–136.
33. Kudsk KA. Evidence for conservative fluid administration following elective surgery. *Annals of Surgery* 2003; **238:** 649–650.
34. Boldt J, Haisch G, Suttner S et al. Are lactated Ringer's solution and normal saline solution equal with regard to coagulation? *Anesthesia and Analgesia* 2002; **94:** 378–384.
35. Virgilio RW, Rice CL, Smith DE et al. Crystalloid vs. colloid resuscitation: is one better? A randomized clinical study. *Surgery* 1979; **85:** 129–139.
36. Lamke LO, Nilsson GE & Reithner HL. Water loss by evaporation from the abdominal cavity during surgery. *Acta Chirurgica Scandinavica* 1977; **143:** 279–284.
37. Jacob M, Chappell D, Conzen P et al. Blood volume is normal after preoperative overnight fasting. *Acta Anaesthesiologica Scandinavica* 2008; **52:** 522–529.
38. Soreide E, Eriksson LI, Hirlekar G et al. Pre-operative fasting guidelines: an update. *Acta Anaesthesiologica Scandinavica* 2005; **49:** 1041–1047.
39. Jacob M, Rehm M, Orth V et al. Exact measurement of the volume effect of 6% hydoxyethyl starch 130/0.4 (Voluven) during acute preoperative normovolemic hemodilution. *Anaesthesist* 2003; **52:** 896–904.
40. Tatara T & Tashiro C. Quantitative analysis of fluid balance during abdominal surgery. *Anesthesia and Analgesia* 2007; **104:** 347–354.
*41. Chan ST, Kapadia CR, Johnson AW et al. Extracellular fluid volume expansion and third space sequestration at the site of small bowel anastomoses. *British Journal of Surgery* 1983; **70:** 36–39.
42. Grocott MP, Mythen MG & Gan TJ. Perioperative fluid management and clinical outcomes in adults. *Anesthesia and Analgesia* 2005; **100:** 1093–1106.
*43. Brandstrup B. Fluid therapy for the surgical patient. *Best Practice & Research. Clinical Anaesthesiology* 2006; **20:** 265–283.
44. Shires T, Williams J & Brown F. Acute change in extracellular fluids associated with major surgical procedures. *Annals of Surgery* 1961; **154:** 803–810.
45. Carrico CJ, Canizaro PC & Shires GT. Fluid resuscitation following injury: rationale for the use of balanced salt solutions. *Critical Care Medicine* 1976; **4:** 46–54.
46. Brandstrup B, Svensen C & Engquist A. Hemorrhage and operation cause a contraction of the extracellular space needing replacement – evidence and implications? A systematic review. *Surgery* 2006; **139:** 419–432.
47. Margarson MP & Soni N. Serum albumin: touchstone or totem? *Anaesthesia* 1998; **53:** 789–803.

48. Joles JA, Rabelink TJ, Braam B & Koomans HA. Plasma volume regulation: defences against edema formation (with special emphasis on hypoproteinemia). *American Journal of Nephrology* 1993; **13:** 399–412.
49. Roth E, Lax LC & Maloney Jr. JV. Ringer's lactate solution and extracellular fluid volume in the surgical patient: a critical analysis. *Annals of Surgery* 1969; **169:** 149–164.
50. Woerlee GM. *Common perioperative problems and the anaesthetist*. Dordrecht: Kluwer Academic Publishers, 1988.
51. Nielsen OM. Extracellular fluid and colloid osmotic pressure in abdominal vascular surgery. A study of volume changes. *Danish Medical Bulletin* 1991; **1991**(38)**:** 9–21.
52. Doty DB, Hufnagel HV & Moseley RV. The distribution of body fluids following hemorrhage and resuscitation in combat casualties. *Surgery Gynecology & Obstetrics* 1970; **130:** 453–458.
53. Jacob M, Conzen P, Finsterer U et al. Technical and physiological background of plasma volume measurement with indocyanine green - a clarification of misunderstandings. *Journal of Applied Physiology* 2007; **102:** 1235–1242.
54. Newton WT, Pease HD & Butcher Jr. HR. Sodium and sulfate distributions in dogs after hemorrhagic shock. *Surgical Forum* 1969; **20:** 1–2.
55. Reid DJ. Intracellular and extracellular fluid volume during surgery. *British Journal of Surgery* 1968; **55:** 594–596.
56. Berson SA & Yalow RS. Critique of extracellular space measurements with small ions: Na24 and Br82 spaces. *Science* 1955; **121:** 34–36.
57. Vineyard G & Osborne D. Simultaneous determination of extracellular water by 35-sulphate and 82-bromide in dogs, with a note on the acute effects of hypotensive shock. *Surgical Forum* 1967; **18:** 37–39.
58. Schloerb P, Peters C, Cage G et al. Evaluation of the sulphate space as a measure of extracellular fluid. *Surgical Forum* 1967; **18:** 39–41.
59. Cleland J, Pluth JR, Tauxe WN & Kirklin JW. Blood volume and body fluid compartment changes soon after closed and open intracardiac surgery. *The Journal of Thoracic and Cardiovascular Surgery* 1966; **52:** 698–705.
60. Anderson RW, Simmons RL, Collins JA et al. Plasma volume and sulfate spaces in acute combat casualties. *Surgery Gynecology & Obstetrics* 1969; **128:** 719–724.
61. Krejcie TC, Henthorn TK, Gentry WB et al. Modifications of blood volume alter the disposition of markers of blood volume, extracellular fluid, and total body water. *The Journal of Pharmacology and Experimental Therapeutics* 1999; **291:** 1308–1316.
62. Herbst Jr. CA. Simultaneous distribution rate and dilution volume of bromide-82 and thiocyanate in body fluid overload: experimental and clinical correlation. *Annals of Surgery* 1974; **179:** 200–208.
63. Roberts JP, Roberts JD, Skinner C et al. Extracellular fluid deficit following operation and its correction with Ringer's lactate. A reassessment. *Annals of Surgery* 1985; **202:** 1–8.
64. Carrico CJ, Coln CD, Lightfoot SA et al. Extracellular fluid volume replacement in hemorrhagic shock. *Surgical Forum* 1963; **14:** 10–12.
65. Shires T, Coln D, Carrico J & Lightfoot S. Fluid therapy in hemorrhagic shock. *Archives of Surgery* 1964; **88:** 688–693.
66. Fukuda Y, Fujita T, Shibuya J & Albert SN. The distribution between the intravascular and interstitial compartments of commonly utilized replacement fluids. *Anesthesia and Analgesia* 1969; **48:** 831–838.
67. Gutelius JR, Shizgal HM & Lopez G. The effect of trauma on extracellular water volume. *Archives of Surgery* 1968; **97:** 206–214.
68. Breckenridge IM, Digerness SB & Kirklin JW. Validity of concept of increased extracellular fluid after open heart surgery. *Surgical Forum* 1969; **20:** 169–171.
69. Breckenridge IM, Digerness SB & Kirklin JW. Increased extracellular fluid after open intracardiac operation. *Surgery Gynecology & Obstetrics* 1970; **131:** 53–56.
70. Gumpert JR, Zollinger RM & Riddell AG. Proceedings: the measurement of extracellular fluid volume with radiobromide simultaneous plasma and lymph disappearance in man. *British Journal of Surgery* 1973; **60:** 903.
71. Kragelund E. Loss of fluid and blood to the peritoneal cavity during abdominal surgery. *Surgery* 1971; **69:** 284–287.
72. Pacifico AD, Digerness S & Kirklin JW. Acute alterations of body composition after open intracardiac operations. *Circulation* 1970; **41:** 331–341.
73. Kragelund E. Changes of the apparent 3HOH, 82Br, 125I human albumin and 51Cr red blood cell dilution volumes before, during and after operation in human subjects. *Annals of Surgery* 1970; **172:** 116–124.
74. Nielsen OM & Engell HC. Extracellular fluid volume and distribution in relation to changes in plasma colloid osmotic pressure after major surgery. A randomized study. *Acta Chirurgica Scandinavica* 1985; **151:** 221–225.
75. Ladegaard-Pedersen HJ & Engell HC. A comparison of the distribution volumes of inulin and (51 Cr)EDTA in man and nephrectomized dogs. *Scandinavian Journal of Clinical and Laboratory Investigation* 1972; **30:** 267–270.
76. Ladegaard-Pedersen H. Inulin distribution volume, plasma volume, and colloid osmotic pressure before and after major surgery. *Acta Chirurgica Scandinavica* 1974; **140:** 505–507.
77. Shizgal HM, Solomon S & Gutelius JR. Body water distribution after operation. *Surgery Gynecology & Obstetrics* 1977; **144:** 35–41.
78. Magner JJ, McCaul C, Carton E et al. Effect of intraoperative intravenous crystalloid infusion on postoperative nausea and vomiting after gynaecological laparoscopy: comparison of 30 and 10 ml kg(-1). *British Journal of Anaesthesia* 2004; **93:** 381–385.
79. Holte K, Kristensen BB, Valentiner L et al. Liberal versus restrictive fluid management in knee arthroplasty: a randomized, double-blind study. *Anesthesia and Analgesia* 2007; **105:** 465–474.
80. Stevens T, Garcia JG, Shasby DM et al. Mechanisms regulating endothelial cell barrier function. *American Journal of Physiology. Lung Cellular and Molecular Physiology* 2000; **279:** L419–L422.
81. Starling E. On the absorption of fluid from the connective tissue spaces. *The Journal of Physiology (London)* 1896; **19:** 312–326.
82. Jackson R, Reid JA & Thorburn J. Volume preloading is not essential to prevent spinal-induced hypotension at caesarean section. *British Journal of Anaesthesia* 1995; **75:** 262–265.
83. Karinen J, Rasanen J, Alahuhta S et al. Effect of crystalloid and colloid preloading on uteroplacental and maternal haemodynamic state during spinal anaesthesia for caesarean section. *British Journal of Anaesthesia* 1995; **75:** 531–535.

84. Kinsella SM, Pirlet M, Mills MS et al. Randomized study of intravenous fluid preload before epidural analgesia during labour. *British Journal of Anaesthesia* 2000; **85:** 311–313.
85. Rout CC, Akoojee SS, Rocke DA & Gouws E. Rapid administration of crystalloid preload does not decrease the incidence of hypotension after spinal anaesthesia for elective caesarean section. *British Journal of Anaesthesia* 1992; **68:** 394–397.
86. Arieff AI. Fatal postoperative pulmonary edema: pathogenesis and literature review. *Chest* 1999; **115:** 1371–1377.
87. Kroll W, Polz W, Colombo T & Steindorfer P. Degree of substitution and volume expanding effect of various medium molecular weight hydroxyethyl starch solutions. *Wiener Klinische Wochenschrift* 1994; **106:** 416–421.
88. Chappell D, Jacob M, Hofmann-Kiefer K et al. Hydrocortisone preserves the vascular barrier by protecting the endothelial glycocalyx. *Anesthesiology* 2007; **107:** 776–784.
*89. Pries AR, Secomb TW & Gaehtgens P. The endothelial surface layer. *Pflügers Archiv* 2000; **440:** 653–666.
90. Rehm M, Zahler S, Lotsch M et al. Endothelial glycocalyx as an additional barrier determining extravasation of 6% hydroxyethyl starch or 5% albumin solutions in the coronary vascular bed. *Anesthesiology* 2004; **100:** 1211–1223.
91. Bruegger D, Jacob M, Rehm M et al. Atrial natriuretic peptide induces shedding of endothelial glycocalyx in coronary vascular bed of guinea pig hearts. *American Journal of Physiology. Heart and Circulatory Physiology* 2005; **289:** H1993–H1999.
92. Jacob M, Bruegger D, Rehm M et al. The endothelial glycocalyx affords compatibility of Starling's principle and high cardiac interstitial albumin levels. *Cardiovascular Research* 2007; **73:** 575–586.
93. Vogel J, Sperandio M, Pries AR et al. Influence of the endothelial glycocalyx on cerebral blood flow in mice. *Journal of Cerebral Blood Flow and Metabolism* 2000; **20:** 1571–1578.
94. Vink H, Constantinescu AA & Spaan JA. Oxidized lipoproteins degrade the endothelial surface layer: implications for platelet-endothelial cell adhesion. *Circulation* 2000; **101:** 1500–1502.
*95. Nieuwdorp M, van Haeften TW, Gouverneur MC et al. Loss of endothelial glycocalyx during acute hyperglycemia coincides with endothelial dysfunction and coagulation activation in vivo. *Diabetes* 2006; **55:** 480–486.
96. Jacob M, Bruegger D, Rehm M et al. Contrasting effects of colloid and crystalloid resuscitation fluids on cardiac vascular permeability. *Anesthesiology* 2006; **104:** 1223–1231.
97. Hu X & Weinbaum S. A new view of Starling's hypothesis at the microstructural level. *Microvascular Research* 1999; **58:** 281–304.
98. Hu X, Adamson RH, Liu B et al. Starling forces that oppose filtration after tissue oncotic pressure is increased. *American Journal of Physiology. Heart and Circulatory Physiology* 2000; **279:** H1724–H1736.
99. Michel CC. Starling: the formulation of his hypothesis of microvascular fluid exchange and its significance after 100 years. *Experimental Physiology* 1997; **82:** 1–30.
100. Adamson RH. Permeability of frog mesenteric capillaries after partial pronase digestion of the endothelial glycocalyx. *The Journal of Physiology* 1990; **428:** 1–13.
101. Chappell D, Hofmann-Kiefer K, Jacob M, et al. TNF-α induced shedding of the endothelial glycocalyx is prevented by hydrocortisone and antithrombin. *Basic Research in Cardiology* 2009; **104:** 78–89.
102. Desborough JP. The stress response to trauma and surgery. *British Journal of Anaesthesia* 2000; **85:** 109–117.
103. Wilmore DW. Metabolic response to severe surgical illness: overview. *World Journal of Surgery* 2000; **24:** 705–711.
104. Kamp-Jensen M, Olesen KL, Bach V et al. Changes in serum electrolyte and atrial natriuretic peptide concentrations, acid-base and haemodynamic status after rapid infusion of isotonic saline and Ringer lactate solution in healthy volunteers. *British Journal of Anaesthesia* 1990; **64:** 606–610.
105. Schutten HJ, Johannessen AC, Torp-Pedersen C et al. Central venous pressure – a physiological stimulus for secretion of atrial natriuretic peptide in humans? *Acta Physiologica Scandinavica* 1987; **131:** 265–272.
106. Brunkhorst FM, Engel C, Bloos F et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *The New England Journal of Medicine* 2008; **358:** 125–139.
107. Finfer S, Bellomo R, Boyce N et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *The New England Journal of Medicine* 2004; **350:** 2247–2256.
108. Chappell D, Jacob M, Paul O et al. The glycocalyx of the human umbilical vein endothelial cell. An impressive structure ex vivo but not in culture. *Circulation Research* 2009; **104:** 1313–1317.