

Intraoperative fluids: how much is too much?

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Editor's key points

- Both too little and excessive fluid during the intraoperative period can adversely affect patient outcome.
- Greater understanding of fluid kinetics at the endothelial glycocalyx enhances insight into bodily fluid distribution.
- Evidence is mounting that fluid therapy guided by flow based haemodynamic monitors improve perioperative outcome.
- It is unclear whether crystalloid or colloid fluids or a combination of both produce the optimal patient outcome and in what clinical context.

Summary. There is increasing evidence that intraoperative fluid therapy decisions may influence postoperative outcomes. In the past, patients undergoing major surgery were often administered large volumes of crystalloid, based on a presumption of preoperative dehydration and nebulous intraoperative 'third space' fluid loss. However, positive perioperative fluid balance, with postoperative fluid-based weight gain, is associated with increased major morbidity. The concept of 'third space' fluid loss has been emphatically refuted, and preoperative dehydration has been almost eliminated by reduced fasting times and use of oral fluids up to 2 h before operation. A 'restrictive' intraoperative fluid regimen, avoiding hypovolaemia but limiting infusion to the minimum necessary, initially reduced major complications after complex surgery, but inconsistencies in defining restrictive vs liberal fluid regimens, the type of fluid infused, and in definitions of adverse outcomes have produced conflicting results in clinical trials. The advent of individualized goal-directed fluid therapy, facilitated by minimally invasive, flow-based cardiovascular monitoring, for example, oesophageal Doppler monitoring, has improved outcomes in colorectal surgery in particular, and this monitor has been approved by clinical guidance authorities. In the contrasting clinical context of relatively low-risk patients undergoing ambulatory surgery, high-volume crystalloid infusion (20–30 ml kg⁻¹) reduces postoperative nausea and vomiting, dizziness, and pain. This review revises relevant physiology of body water distribution and capillary-tissue flow dynamics, outlines the rationale behind the fluid regimens mentioned above, and summarizes the current clinical evidence base for them, particularly the increasing use of individualized goal-directed fluid therapy facilitated by oesophageal Doppler monitoring.

Keywords: fluid therapy; fluids, i.v.

Fluid therapy is fundamental to the practice of intraoperative anaesthesia, but the precise type, amount, and timing of its administration is still the subject of extensive debate. Almost all patients presenting for general anaesthesia will be administered some form of i.v. fluid. Evidence is increasing that perioperative fluid therapy can affect important longer-term postoperative outcomes. Traditional practice involving intraoperative administration of large crystalloid fluid volumes to all patients are being challenged by recent evidence-based, individualized goal-directed therapy (GDT). Although many research questions about the balance of crystalloid and colloid fluid remain unanswered, current research is focusing on gaining greater understanding of fluid movement at the vascular barrier and how surgery and anaesthetic interventions can influence it in the intraoperative period.

This review revises the relevant physiology underpinning body fluid distribution and capillary flow dynamics. It also discusses the current evidence-based rationale for using

various volumes and types of fluid therapy in different intraoperative clinical contexts. Discussion of preoperative fluid resuscitation and continuing postoperative fluid therapy is outside the scope of this review.

Physiology

Body water distribution

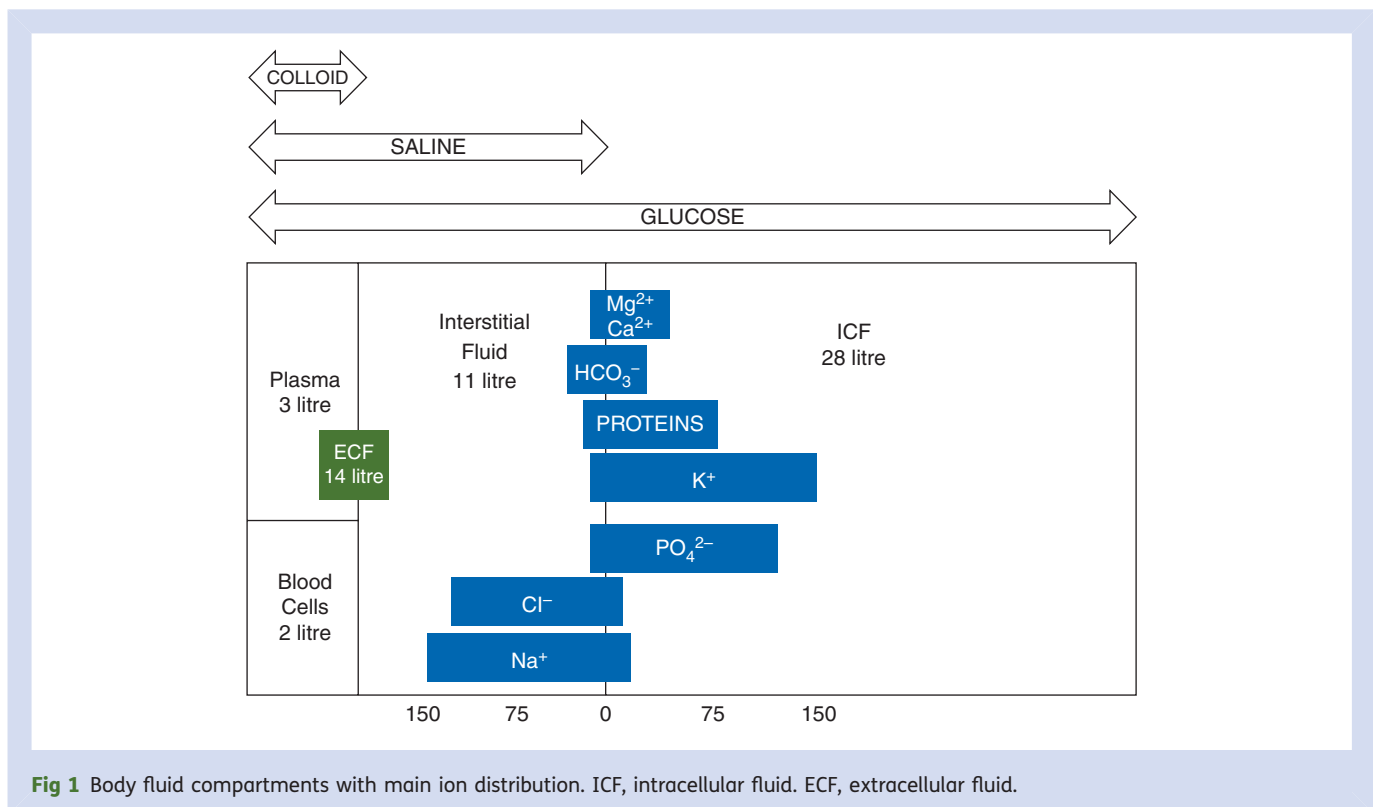
Water comprises 60% of the lean body mass, ~42 litres in a 70 kg man. Of this, about two-thirds are intracellular (28 litres); therefore, extracellular volume (ECV) comprises 14 litres. The extracellular compartment can be further divided into interstitial (11 litres) and plasma (3 litres) with small amounts of transcellular fluids, for example, intraocular, gastrointestinal secretion, and cerebrospinal fluid completing the distribution (Fig. 1). These transcellular fluids are considered anatomically separate and not available for water and solute exchange.¹

Total body water (TBW) can be estimated by using dilution tracer techniques. Isotopically labelled water using deuterium or tritium diffuses through the TBW compartment. Extracellular fluid (ECF) measurement requires that the marker used must cross capillaries but not cell membranes. Radiolabelled sulphate ($^{35}\text{SO}_4^{2-}$) or bromide ($^{82}\text{Br}^-$) ions are the most commonly used extracellular tracers. Intracellular fluid volume (ICV) is calculated indirectly by subtracting ECV from TBW. The intravascular volume can be measured using radiolabelled albumin or with the dye Evans Blue. Interstitial volume is then calculated by subtracting intravascular volume from ECV.

The capillary endothelium is freely permeable to water, anions, cations, and other soluble substances such as glucose but is impermeable to protein and other large molecules >35 kDa, which are largely confined to the intravascular space.² In the ECF, Na^+ is the principal cation and Cl^- the main anion. In contrast, in the intracellular compartment, K^+ is the major cation and PO_4^{2-} the principal anion, with a high protein content.³ As the cellular membrane is freely permeable to water but not to ions, osmotic equilibrium is maintained. In a healthy individual, daily fluctuations in TBW are small ($<0.2\%$) and are finely balanced with modifications of thirst mechanisms and fluid balance, controlled by the renin-angiotensin anti-diuretic and atrial natriuretic peptide (ANP) hormone systems. The basal fluid requirement in a normothermic adult with a normal metabolic rate is $1.5 \text{ ml kg}^{-1} \text{ h}^{-1}$.

Capillary tissue fluid dynamics

Fluid shifts between the intravascular and remainder of the extracellular space occurs at the vascular endothelial barrier. The forces governing this were described by Starling⁴ in 1896 and remain the basis of our understanding of fluid movement in the microvasculature. The fluid components of the blood are contained within the vessels of the microcirculation mainly by the inward pull of colloid osmotic pressure (COP) produced by the protein content of the plasma (Fig. 2). This opposes the high outward hydrostatic pressure, which tends to push plasma out of the vessels and into the interstitium. Both the hydrostatic and colloid osmotic pressure in the interstitium are low. The net result of these forces is a small outward leak of fluid and protein from the vasculature to the interstitium which is continually returned to the blood vessels via the lymphatic system.⁵ The vascular endothelium is permeable to water but impermeable to protein and other large molecules. Movement across the vascular endothelium of small molecules such as sodium, potassium, chloride, and glucose occurs freely across specialized pathways between the endothelial cells. Macromolecule transport may occur via large pores in the endothelium or by transport by vesicles.² Fluid movement across the capillary endothelium can be classified into two types. Type 1 (physiological) occurs continuously with an intact vascular barrier and is returned to the vascular compartment by the lymphatic system, thereby avoiding interstitial oedema. Type 2 (pathological) fluid movement occurs when the vascular barrier becomes



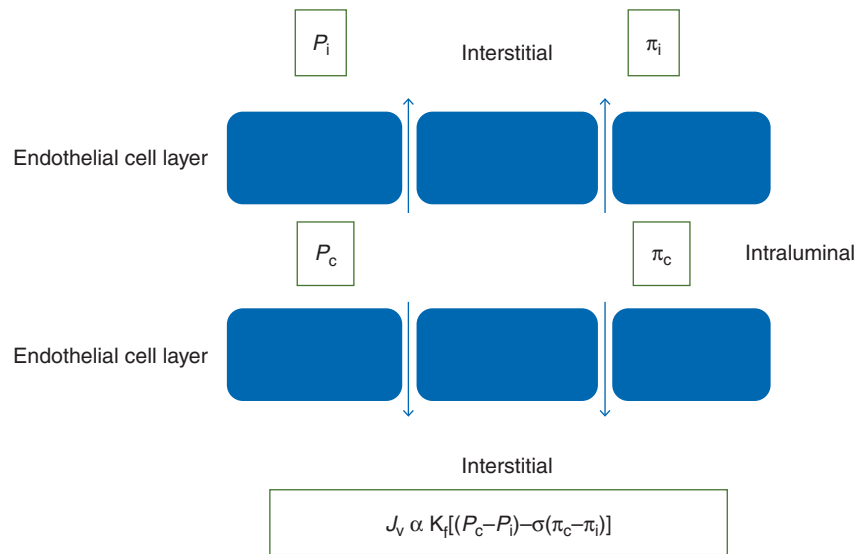


Fig 2 Classic Starling equation with net efflux of fluid to the interstitial space. J_v , net filtration; K_f , filtration coefficient; P_c , capillary hydrostatic pressure; P_i , interstitial hydrostatic pressure; σ , reflection coefficient; π_c , capillary oncotic pressure; π_i , interstitial oncotic pressure.

damaged or dysfunctional, allowing excessive fluid accumulation leading to interstitial oedema.⁶

The endothelial glycocalyx

Recent research has expanded our understanding of fluid movement at the endothelial barrier. The endothelium is one cell thick and is coated on its luminal side with a fragile layer, the glycocalyx, which provides a first line barrier to regulating cellular and macromolecule transport at the endothelium.⁷ The endothelial glycocalyx layer (EGL) is composed of membrane-bound glycoproteins and proteoglycans and contains glycosaminoglycans. It creates an exclusion zone for erythrocytes, therefore non-circulating, protein-rich plasma predominates within it. The intravascular volume consists of the glycocalyx volume, plasma volume, and the red cell distribution volume.⁸ Together the glycocalyx and endothelial cells comprise the endothelial surface layer (ESL). The ESL is 0.4–1.2 μm thick and is in dynamic equilibrium with the circulating plasma. To function, the ESL requires a normal level of plasma albumin.⁹ Current theory promotes a ‘double barrier concept’ where both the endothelial cell layer and the EGL play a role in maintaining the vascular barrier.^{10 11}

Improved understanding of microvascular physiology allows explanation of the discrepancy between clinical findings during fluid therapy and the original Starling principle.⁸ Transendothelial pressure difference and the plasma subglycocalyx colloid oncotic pressure difference are central to fluid filtration, with interstitial COP negligible. At subnormal capillary pressure, transcapillary flow approaches zero. When capillary pressure is supranormal, the COP is maximal and fluid movement is dependent on transendothelial pressure

difference. When a colloid solution is infused in this situation, it distributes through the plasma volume, maintaining COP while increasing capillary pressure and therefore fluid filtration increases. A crystalloid solution in the same situation distributes throughout the intravascular volume and increases capillary pressure but lowers COP, so fluid filtration is increased more than with a colloid. When capillary pressure is low, both types of fluid are retained in the intravascular space until the transendothelial pressure increases to the point where transcapillary flow resumes. This physiological model therefore supports the use of crystalloid infusion over colloid for resuscitation while colloids have a role in euvoalaemic or hypervolaemic haemodilution. As the red cell volume is less than intravascular volume, studies using this parameter as an endpoint need to be interpreted with caution.

The endothelium is not only a barrier between the blood and tissues but also has roles in primary haemostasis, coagulation, fibrinolysis, inflammation, and regulation of vasomotor tone.⁷ Numerous factors have been shown to damage the endothelial glycocalyx causing platelet aggregation, leucocyte adhesion, and increased vascular permeability leading to interstitial oedema. These factors^{12–17} are summarized in Table 1.

Perioperative protection of the endothelial glycocalyx is a plausible strategy for prevention of interstitial oedema. Experimental studies have shown that pretreatment with hydrocortisone and antithrombin preserve the integrity of the endothelium by reducing shedding of the glycocalyx and adhesion of leucocytes after ischaemia/reperfusion injury.¹⁸ Sevoflurane also shows protective effects by stabilizing the endothelial glycocalyx and diminishing adhesion of

Table 1 Factors affecting the endothelial glycocalyx—known injurious mechanisms and potential protective agents

Degradation	Protection
Ischaemia/reperfusion; hypoxia/reoxygenation; inflammatory cytokines proteases; atrial natriuretic peptide	Sevoflurane; hydrocortisone; antithrombin

leucocytes and platelets after ischaemia/reperfusion injury in the isolated guinea pig heart.¹⁹ There are currently no pharmacological agents that increase synthesis or directly prevent enzymatic degradation of the glycocalyx. Therefore, avoiding precipitants of glycocalyceal damage and incorporation of potentially protective agents (Table 1) should be considered.²⁰

Distribution of crystalloid fluid

The composition of fluid infused to a patient determines its bodily distribution. When 1 litre glucose 5% is administered, the glucose is metabolized in the liver, leaving only water which distributes to the ECV and ICV in proportion to the volume infused. Therefore, only 7% (about 70 ml) remains in the vascular compartment after equilibration with the other body fluid compartments, because plasma comprises 3 of 42 litres TBW. Infusion of an isotonic sodium containing solution on the other hand is confined to the extracellular space because sodium is prevented from traversing the intracellular space by the cell membrane. Therefore, when 1 litre of 0.9% saline is administered, 20% should remain in the vascular compartment after equilibration with the other body fluid compartments as the plasma compartment accounts for 20% of ECF.

However, the effects of different types of both colloid and crystalloid solutions have been studied in healthy volunteers, hypovolaemic states, and diseased states. Eighteen healthy volunteers received 50 ml kg⁻¹ lactated Ringer's (LR) solution and 0.9% saline (NS) on two separate occasions.²¹ It was found that LR transiently decreased serum osmolality which returned to baseline 1 h later. NS did not affect serum osmolality but caused metabolic acidosis. Lobo and colleagues²² performed a double-blind, crossover study on 10 healthy male volunteers to investigate the effect of bolus of crystalloid on serum albumin. Each was given 2 litres 0.9% saline and dextrose 5% on two separate occasions in random order. With both solutions, serum albumin was decreased which was accounted for by dilution alone and indicates redistribution within fluid compartments. The decrease in albumin was prolonged >6 h with NS, but levels had returned to baseline 1 h after infusion with dextrose. Haemoglobin also decreased in proportion to the dilutional effect. The water load from the dextrose infusion was excreted 2 h post infusion, but NS had a persistent diluting effect with only 30% of both sodium and water being

excreted at 6 h. Similar endpoints were assessed in a study comparing 0.9% saline with Hartmann's solution.²³ Plasma expansion was shown to be more sustained with NS than Hartmann's, as estimated by dilution of haemoglobin and albumin. The NS group retained 56% of infused volume at 6 h compared with 30% for Hartmann's, based on body weight. There were no significant differences in serum potassium, sodium, urea, or total osmolality. In the NS group, bicarbonate levels were lower and all subjects were hyperchloraemic, which was sustained >6 h. These biochemical changes place the body under physiological stress to eliminate the supranormal electrolyte load and may adversely affect organ function and surgical outcome.^{22 24–26}

Distribution of colloid

Colloid fluids contain macromolecules (usually >40 kDa) such as polysaccharides or polypeptides from either plant or animal sources and are used as plasma expanders. To prevent haemolysis, the macromolecules are suspended in an electrolyte solution which may be 0.9% sodium chloride or a more balanced solution similar to Hartmann's. Because they contain larger molecules which cannot pass the endothelium, they remain in the plasma longer than crystalloids. Unlike crystalloid solutions, colloids carry a risk of anaphylaxis, have a dose-dependent effect on coagulation and molecules may be deposited in tissues causing pruritis.²⁷ On the other hand, there is evidence showing a beneficial effect of plasma expanders on inflammation, the microcirculation, and endothelial activation.

Studies have shown that colloid administration is context-sensitive. Despite the large molecules in these solutions, which should confine them to the vascular compartment, volume loading with both 6% hydroxyethyl starch (HES) and albumin 5% in the normovolaemic patient resulted in 68% of the infused volume extravasating the intravascular space into the interstitium within minutes. Conversely, when 6% HES or albumin 5% was given in the context of normovolaemic haemodilution, the volume remaining in the intravascular space approached 90%.²⁸

The effect of volume loading with 0.9% saline, 0.4% succinylated gelatine (gelifusine), and 6% hydroxyethyl starch (voluven) on blood volume and endocrine response in healthy volunteers was recently investigated.²⁹ After completion of a 1 h infusion, 68%, 21%, and 16% of 0.9% saline, gelifusine, and voluven, respectively, had leaked from the intravascular space. Blood volume calculations were based on haematocrit dilution. There was little difference between both colloids, even though they have wide ranging average molecular weights (gelifusine 30 kDa, voluven 130 kDa). This may reflect the different handling of small and large molecules in the microvasculature.

The renin-angiotensin-aldosterone system (RAAS) is fundamental to the regulation of sodium excretion after a sodium load. All three solutions had similar effects on renin secretion, with levels of both renin and aldosterone being

reduced. Brain natriuretic peptide (BNP) was also measured and showed an increase in all three groups 1 h after commencement of the infusion. This correlates with other works indicating the role of BNP and ANP in acute hypervolaemia.³⁰ It was concluded that the excretion of the sodium and chloride load may depend on suppression of the RAAS and not on natriuretic peptides.

It is commonly believed that intravascular losses require 3–4 times volume replacement with crystalloid fluids compared with colloids. A recent systematic review of the use of HES in surgical, emergency, and intensive care patients reported that the crystalloid to colloid ratio for volume resuscitation was lower, <2:1.³¹ This may reflect the increased vasopermeability to colloid that has been observed in the clinical setting. However, fluid loading with colloid showed a greater linear increase in cardiac filling, cardiac output, and stroke work in both septic and non-septic patients when compared with normal saline.³² Also, in a randomized trial of HES and NS in trauma patients, HES showed greater lactate clearance and less renal injury when compared with NS in patients with penetrating injuries.³³

Traditional practice of intraoperative fluid administration

The aim of intraoperative fluid therapy is to maintain an adequate circulating volume to ensure end-organ perfusion and oxygen delivery to the tissues. Traditionally, this was achieved by routine infusion of large volumes of crystalloid. This was based on the outdated premise that the preoperative patient was hypovolaemic due to prolonged fasting ('nil by mouth after midnight') and cathartic bowel preparation, in addition to ongoing losses from perspiration and urinary output. There was also a widespread belief that surgical exposure required aggressive replacement of insensible fluid loss, often termed 'third space' losses. Further, hypotension during general and neuraxial anaesthesia often triggered compensatory liberal i.v. fluid administration. However, fluid loading has no influence on anaesthesia-related hypotension^{34 35} and should more appropriately be treated with vasopressor therapy.³⁶

Prolonged preoperative fasting ought no longer feature in modern perioperative care. For over a decade, research has clearly shown that fasting from solid food for 6 h and oral fluid, even containing carbohydrate, for only 2 h before operation, is safe and actually improves outcomes.^{37 38} Studies have shown that in fact, in healthy cardiopulmonary patients, blood volume is normal even after prolonged fasting.³⁶ The use of mechanical bowel preparations has also diminished as evidence shows minimal difference in surgical conditions where this is used.³⁹

The phantom 'third space'

The concept of a 'third space' for body fluids (in addition to intracellular and ECF compartments) was introduced in the 1960s.⁴⁰ Using outdated sulphate tracer techniques, the ECV was measured in patients undergoing major abdominal

surgery. It was concluded that there was a decrease in ECV which was not fully accounted for by the measured blood loss. To explain this, it was hypothesized that fluid was sequestered in areas that became known as the 'third space'. Its location was unknown but speculated to include traumatized tissue or the gastrointestinal tract. Despite this highly implausible concept, lacking any credible supportive scientific or clinical evidence, the practice of aggressive replacement of this hypothetical fluid loss gained widespread traction in intraoperative anaesthetic practice. Infusion of large volumes of crystalloid infusions intraoperatively became standard clinical practice.¹⁰ Consequently, it was not uncommon for postoperative patients to have 7–10 kg weight gain, with proportionately increased risk of all-cause morbidity and mortality.^{41 42} In a systematic review of trials measuring ECV changes, it was concluded that the original data and methodology supporting the concept of third space were fundamentally flawed.⁴³

In the intraoperative patient, maintenance fluids should be infused using balanced crystalloid infusions. More than 30 yr ago, direct measurements of basal evaporation rate from the skin and airway during surgery showed that topical fluid loss is 0.5–1.0 ml kg⁻¹ h⁻¹ during major abdominal surgery.⁴⁴ In the absence of major haemorrhage, large volume fluid loading is contraindicated, because it may lead to hypervolaemia causing ANP release and damage to the endothelial glycocalyx, with detrimental interstitial oedema.

'Restrictive' fluid regimen

In thoracic surgery, fluid restriction is the standard practice, but the intraoperative fluid volume in the general surgical population is widely variable. A randomized, multicentre trial comparing liberal and restrictive fluid regimens in 141 patients undergoing colorectal surgery was undertaken.⁴⁵ The restrictive group received a mean volume of 2.7 litres and the liberal 5.4 litres. The number of patients with postoperative complications was significantly reduced in the restrictive group, 33% vs 51% $P=0.02$. Outcomes assessed included anastomotic leakage, wound infection, and cardiovascular and pulmonary complications. There was no observed increase in renal complications in the restrictive group. However, the two groups received different fluids with the restrictive group receiving a greater amount of colloid and the liberal group, normal saline.

In 2009, a review of restrictive vs liberal fluid therapy and its effect on postoperative outcome⁴⁶ identified seven randomized trials, six involving major abdominal surgery and one involving knee arthroplasty. The trials excluded high-risk patients. The range of fluid administered in the liberal groups was from 2750 to 5388 ml and in the restrictive groups from 998 to 2740 ml. This highlights the fact that no common definition of 'liberal' or 'restrictive' protocols exists in clinical practice. A restrictive regime in one centre may actually be liberal in another. The studies varied in terms of design, types of fluid administered, indications for

administering additional fluid, outcomes variables, and definitions of intra- and postoperative periods. Therefore, there is difficulty interpreting the results. Three of the trials showed improved outcome after restrictive fluid regimes. Two showed no difference in outcome and two showed differences in some selected outcomes only. The studies showing improved outcome with restrictive fluid regimen reported faster return of gastrointestinal function and reduced hospital length of stay (LOS). These studies used colloid and crystalloid infusion. The studies which showed no difference in outcome used crystalloid fluids alone, without colloids. In one study,⁴⁷ both restrictive and liberal fluid regimens received relatively restricted amounts of fluid (mean 2.6 vs 2.0 litres), suggesting that the standard group did not receive the excessive amounts of fluid known to cause harm.

Two further randomized double-blind studies showed benefits to both restrictive and liberal fluid regimes in different clinical context.^{48 49} Both studies used crystalloid and colloid. In the study looking at patients undergoing major colonic surgery, the restrictive fluid regimen demonstrated a beneficial effect in pulmonary function and postoperative hypoxaemia. There was an overall decrease in the number of postoperative complications, but the number of patients with complications was not significantly reduced. There was no difference in other outcome variables such as pain, nausea, and LOS. In the second study, similar fluid regimens were used in patients undergoing knee arthroplasty. Results showed significant hypercoagulability 1–2 days post-procedure in the liberal group and a reduction in post operative nausea and vomiting. There was no difference in the LOS. Taken together, it was concluded that due to inconsistent definitions of both liberal and restrictive fluid regimens and lack of standardization of clinical and physiological outcome measurement, no evidence-based guidelines for procedure-specific perioperative fluid therapy could be issued. This view, in combination with other published research in liberal vs restrictive fluid therapy, suggests that 'one approach fits all' is not appropriate for fluid management in high-risk surgical patients.

High-volume crystalloids for ambulatory moderate-risk surgery

In the contrasting clinical context of minor or moderate surgery in low risk, ambulatory patient, a more liberal strategy seems to be beneficial. Major morbidity is rarely seen in this group of patients, but the rapid return of vital function is crucial to the successful management of the ambulatory patient, allowing timely discharge from hospital. Up to 20–30 ml kg⁻¹ of crystalloid fluid to a healthy adult having low-risk surgery or day-case procedure reduces postoperative complications such as dizziness, drowsiness, pain, nausea, and vomiting.^{50 51} In moderate surgery, Holte and colleagues⁵² evaluated patients undergoing laparoscopic cholecystectomy and compared the effect of 40 and 15 ml kg⁻¹ of LR solution intraoperatively. They found an enhanced

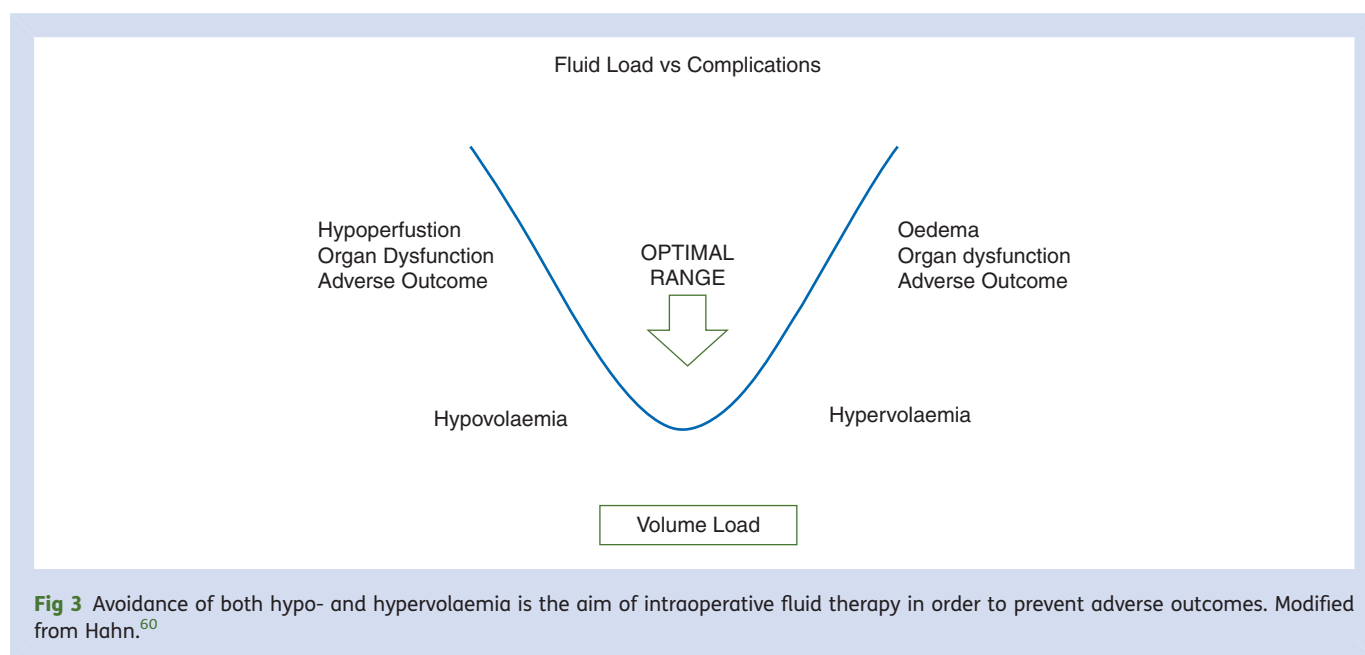
recovery profile with less nausea, dizziness, and drowsiness and improved general wellbeing in those receiving liberal amounts of fluid and a reduced LOS. Studies in major surgery favour a restrictive regime,^{53 54} but this is not a universal finding.⁵⁵ One investigation using bioelectrical impedance measurements in 30 patients undergoing abdominal surgery developed a mathematical model which showed that infusion rates of between 2 and 18.5 ml kg⁻¹ h⁻¹ in surgery of duration <3 h did not cause significant interstitial oedema, but in surgery lasting >6 h, the therapeutic window narrowed to between 5 and 8 ml kg⁻¹ h⁻¹, after which a significant increase in interstitial fluid was seen.⁵⁶

Individualized goal-directed fluid therapy

In recent times, evidence is mounting that outcomes may be improved if fluid therapy is individualized based on objective feedback on the patient's individual fluid responsiveness. This is derived from the old physiological principle of the Frank–Starling curve. This has become known as individualized 'GDT'.⁵⁷ Traditional measurements do not have the ability to adequately identify and guide fluid therapy. A healthy patient may lose up to 25% of blood volume before there is a decrease in arterial pressure or an increase in heart rate, whereas more sensitive monitors may show decreased stroke volume and gastric mucosal pH, indicating ischaemia.⁵⁸ A systematic review of the role of central venous pressure (CVP) measurement in fluid therapy concluded that neither the CVP number nor the rate of change of CVP was accurate in assessing blood volume or in predicting the response to a fluid challenge. Therefore, caution should be exercised in interpreting CVP data to guide fluid administration.⁵⁹

Both hypovolaemia and hypervolaemia are known to cause increased perioperative morbidity and mortality; therefore, assessment of the patients actual haemodynamic status can guide appropriate therapy (Fig. 3).⁶⁰ In the 1980s, GDT required the use of pulmonary artery catheters (PACs) to measure tissue oxygen delivery in high-risk surgical patients, in order to achieve 'supranormal oxygen delivery' with a view to improving outcome.⁶¹ While initial results were encouraging, this technique relied on the widespread use of the PAC. Unfortunately, it quickly became clear that the PAC itself caused increased major morbidity and mortality, which undermined interest in the concept of using physiological targets to optimize cardiovascular performance and improve outcomes.

Over the intervening years, less invasive methods of monitoring flow-based haemodynamic parameters have been developed. Minimally invasive monitors include oesophageal Doppler monitoring and arterial waveform analysis (stroke volume variation, pulse pressure variation—PPV). Other methods require both arterial and central venous access to measure cardiac output. Both the LiDCO and PiCCO systems use pulse contour analysis to measure stroke volume after initial calibration with either lithium (LiDCO) or thermal indicators (PiCCO). The Flotrac/Vigileo system also analyses pulse



contour but does not require calibration which instead is based on a computer program after input of biometric data. It requires only a peripheral arterial line, foregoing the need for central access. While these methods have been validated against gold standard invasive monitoring (i.e. PAC), many have limiting factors in clinical situations. Outcome study results vary from improved outcome in 40 patients receiving regional anaesthesia for hip arthroplasty⁶² to no difference in outcome in 60 patients undergoing peripheral vascular surgery.⁶³ A recent systematic review and meta-analysis looked at the use of pre-emptive haemodynamic intervention in moderate- to high-risk patients to improve postoperative outcomes. Twenty-nine studies were identified which used various forms of haemodynamic monitors, including PAC, LiDCO, PiCCO, FloTrac, and PPV. Intervention consisted of fluid therapy with or without inotrope support. It was concluded that with pre-emptive haemodynamic monitoring guiding therapy, the rate of surgical morbidity and mortality was significantly improved.⁶⁴

The role of fluid maintenance rates in the setting of GDT has been recently analysed. A prospective randomized trial of 88 high-risk patients undergoing major surgery was conducted. The restrictive received a background rate of 4 ml kg⁻¹ h⁻¹ and the conventional 8 ml kg⁻¹ h⁻¹ of Ringer's lactate solution. The LiDCO monitoring system was used to guide intervention with fluid bolus of colloid (gelatine) and inotropes. It was concluded that the restrictive regime during optimization of haemodynamic parameters reduced major complications in older patients with co-morbidities undergoing major surgery.^{65 66} In the intraoperative setting, however, the most promising minimally invasive technique of measuring dynamic cardiovascular performance is the use of the oesophageal Doppler monitor (ODM), which is supported by the most evidence.^{67 68}

Oesophageal Doppler monitoring

Oesophageal Doppler monitoring uses Doppler ultrasound technology to analyse the blood flow in the descending aorta. A disposable probe is inserted into the oesophagus and aligned with the blood flow to produce a flow velocity profile for each heartbeat. The waveform produced is then used in conjunction with a nomogram of biometric data to derive a value for stroke volume. The stroke volume can be used to indicate volume responsiveness. The management of fluid therapy uses an algorithm to maximize cardiovascular contractility, based on the Frank–Starling curve and using bolus of colloid as the intervention. For example, if baseline stroke volume is increased >10% by a fluid bolus of 3 ml kg⁻¹, that patient's heart is fluid responsive, and further fluid boluses may be administered until the increase in stroke volume is <10% of what it was before the previous bolus (Fig. 4). At this point, the patient is on the 'plateau' part of the Frank–Starling curve and fluid boluses should be withheld until the patient's volume status is re-evaluated.

A number of randomized clinical trials in cardiac, orthopaedic, and abdominal surgery evaluated postoperative outcome with oesophageal Doppler-guided fluid therapy. In cardiac surgery, the use of ODM was associated with decreased LOS, fewer complications, and decreased gastric acidosis.⁶⁹ Two studies evaluated oesophageal Doppler use in patients undergoing repair of proximal femur fracture under general anaesthesia.^{70 71} Sinclair and colleagues compared its use in 40 patients with standard intraoperative fluid management and showed a reduced LOS and faster time to medical fitness for discharge in patients who received oesophageal Doppler monitoring. Ninety patients undergoing major abdominal surgery were randomized by Venn and

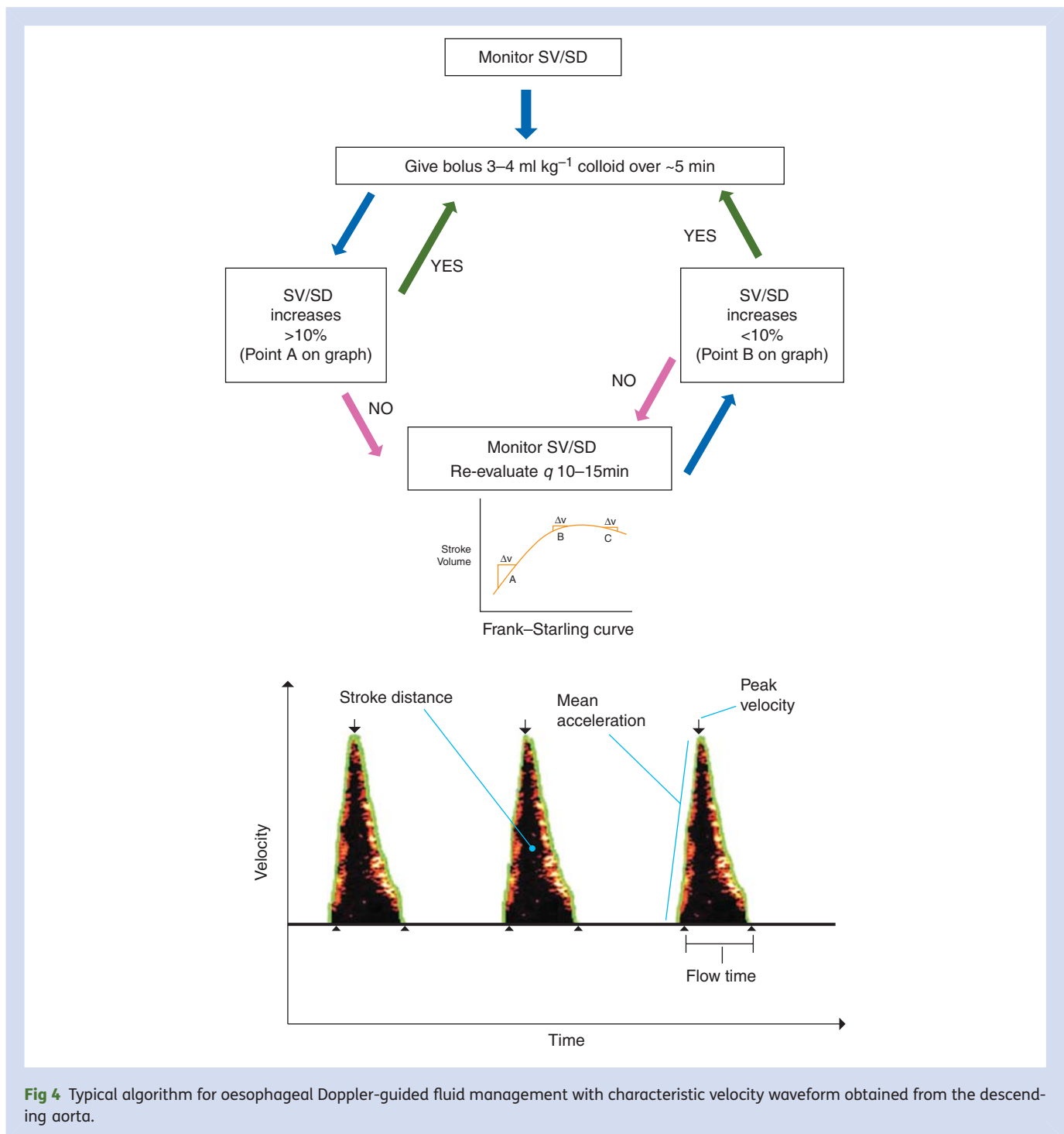


Fig 4 Typical algorithm for oesophageal Doppler-guided fluid management with characteristic velocity waveform obtained from the descending aorta.

colleagues to receive standard treatment, CVP-guided fluid therapy, or oesophageal Doppler-guided management. Oesophageal Doppler and CVP patients had faster time to being medically fit for discharge. However, this study showed no difference in major morbidity and mortality or overall LOS. Meta-analyses of oesophageal Doppler in major abdominal surgery have shown that it is associated with fewer postoperative complications, reduced intensive care unit admission, reduced LOS, and faster return of

gastrointestinal function.^{72 73} No difference was found in the amount of crystalloid fluid administered between the groups, but oesophageal Doppler patients received more colloid. These positive outcome studies resulted in the oesophageal Doppler being recommended for use in major colorectal surgery patients in the UK (NICE, GIFTASUP),^{74 75} the USA (Medicare and Medicaid),⁷⁶ and Europe (Enhanced Recovery After Surgery—ERAS).⁷⁷ These guidelines, however, do not dictate the type of fluid to be used with

ODM and on review of the literature, the optimal type of fluid has not been established and requires further research.⁷⁸

In addition, oesophageal Doppler fluid management has not been directly compared with the restrictive fluid regimen discussed above. One trial studied GDT for laparoscopic colorectal surgery in the setting of an enhanced recovery programme.⁷⁹ Sixty-four patients were randomized into three groups: standard care, GDT with balanced crystalloid, and GDT with colloid in a balanced crystalloid carrier. This study found that there were increased complications and increased LOS in the colloid group. LOS was unconventionally reported in hours and when measured in days, there was no difference between the groups. Complications were not clearly defined. A recent review of published trials of oesophageal Doppler-guided fluid therapy in colorectal surgery, which included this negative trial, concluded that its use improves outcomes, but the large benefits shown in earlier trials may be offset somewhat by advances in perioperative care and surgical technique.⁸⁰ A more recent double-blind trial of aerobically fit and unfit patients undergoing colorectal surgery, randomly assigned each group to receive either ODM-guided GDT or standard fluid management. Results showed that GDT patients gained no additional benefit over standard fluid therapy, and furthermore, the fit subgroup tended to have an increased LOS. It is possible that the risk of iatrogenic fluid overload with GDT may prolong hospital stay.⁸¹

Conclusion and further research questions

Past practice in intraoperative fluid therapy was too often influenced by anecdotal reports and tradition than rigorous scientific and clinical investigation. Modern evidence-based practice suggests that intraoperative fluid therapy should be tailored to two broad clinical contexts: In the low-risk patient undergoing low risk or ambulatory surgery, high-volume crystalloid infusions of the order of 20–30 ml kg⁻¹ (e.g. 2 litres over 30 min to the average adult) improves ambulatory anaesthesia outcomes such as pain, nausea, dizziness, and increases street readiness.

On the other hand, high-risk patients undergoing major surgery seem to benefit from a 'restrictive' fluid regimen. This remains to be clearly defined, but a good working definition in a patient with normal renal function would be that intraoperative urine output is kept between 0.5 and 1.0 ml kg⁻¹ h⁻¹. Further individualized fluid guidance is obtained from goal-directed fluid therapy using minimally invasive oesophageal Doppler technology, which has recently been approved by regulatory bodies in the UK, Europe, and the USA. Increasing availability and application of this technology into routine practice in the years to come should facilitate improved outcomes in the context of accelerated recovery clinical pathways.

It remains to be elucidated, however, whether colloid or crystalloid or a balance between these types of fluid produces optimum outcomes and in what particular clinical scenarios. Such clinical questions will provide fertile

grounds for ongoing randomized controlled trials in this area for many years to come.

Declaration of interest

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References

- 1 Kaye A, Riopelle J. Intravascular fluid and electrolyte physiology In: Miller R, ed. *Miller's Anesthesia*, vol. 54, 7th Edn. Philadelphia: Churchill Livingstone, 2009; 1705–7
- 2 Michel CC. Transport of macromolecules through microvascular walls. *Cardiovasc Res* 1996; **32**: 644–53
- 3 Ganter T, Hofer C, Pittet J. Postoperative intravascular therapy. In Miller R, ed. *Miller's Anesthesia*, vol. 88, 7th Edn. Philadelphia: Churchill Livingstone, 2009; 2783–7
- 4 Starling EH. On the absorption of fluids from the connective tissue Spaces. *J Physiol* 1896; **19**: 312–26
- 5 Strunden MS, Heckel K, Goetz AE, Reuter DA. Perioperative fluid and volume management: physiological basis, tolls and strategies. *Ann Intensive Care* 2011; **1**: 2
- 6 Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M. A rational approach to perioperative fluid management. *Anesthesiology* 2008; **109**: 723–40
- 7 Ait-Oufella H, Maury E, Lehoux S, Guidet B, Offenstadt G. The endothelium: physiological functions and role in microcirculatory failure during severe sepsis. *Intensive Care Med* 2010; **36**: 1286–98
- 8 Woodcock TE, Woodcock TM. Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. *Br J Anaesth* 2012; **108**: 384–94
- 9 Jacob M, Bruegger D, Rehm M, et al. The endothelial glycocalyx affords compatibility of Starling's principle and high cardiac interstitial albumin levels. *Cardiovasc Res* 2007; **73**: 575–86
- 10 Jacob M, Chappell D, Rehm M. The 'third space'—fact or fiction? *Best Pract Res Clin Anaesthesiol* 2009; **23**: 145–57
- 11 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**: 1211–23
- 12 Chappell D, Jacob M, Hofmann-Kiefer K, et al. Hydrocortisone preserves the vascular barrier by protecting the endothelial glycocalyx. *Anesthesiology* 2007; **107**: 776–84
- 13 Annecke T, Fischer J, Hartmann H, et al. Shedding of the coronary endothelial glycocalyx: effects of hypoxia/reoxygenation vs ischaemia/reperfusion. *Br J Anaesth* 2011; **107**: 679–86
- 14 Henry CB, Duling BR. TNF-alpha increases entry of macromolecules into luminal endothelial cell glycocalyx. *Am J Physiol Heart Circ Physiol* 2000; **279**: H2815–23
- 15 Chappell D, Jacob M, Becker BF, Hofmann-Kiefer K, Conzen P, Rehm M. Expedition glycocalyx. A newly discovered 'Great Barrier Reef'. *Anaesthetist* 2008; **57**: 959–69
- 16 Bruegger D, Schwartz L, Chappell D, et al. Release of atrial natriuretic peptide precedes shedding of the endothelial glycocalyx equally in patients undergoing on- and off-pump coronary artery bypass surgery. *Basic Res Cardiol* 2011; **106**: 1111–21
- 17 Desborough JP. The stress response to trauma and surgery. *Br J Anaesth* 2000; **85**: 109–17

- 18 Chappell D, Dorfler N, Jacob M, et al. Glycocalyx protection reduces leukocyte adhesion after ischemia/reperfusion. *Shock* 2010; **34**: 133–9
- 19 Chappell D, Heindl B, Jacob M, et al. Sevoflurane reduces leukocyte and platelet adhesion after ischemia–reperfusion by protecting the endothelial glycocalyx. *Anesthesiology* 2011; **115**: 483–91
- 20 Becker BF, Chappell D, Bruegger D, Annecke T, Jacob M. Therapeutic strategies targeting the endothelial glycocalyx: acute deficits, but great potential. *Cardiovasc Res* 2010; **87**: 300–10
- 21 Williams EL, Hildebrand KL, McCormick SA, Bedel MJ. The effect of intravenous lactated Ringer's solution versus 0.9% sodium chloride solution on serum osmolality in human volunteers. *Anesth Analg* 1999; **88**: 999–1003
- 22 Lobo DN, Stanga Z, Simpson JA, Anderson JA, Rowlands BJ, Allison SP. Dilution and redistribution effects of rapid 2-litre infusions of 0.9% (w/v) saline and 5% (w/v) dextrose on haematological parameters and serum biochemistry in normal subjects: a double-blind crossover study. *Clin Sci Lond* 2001; **101**: 173–9
- 23 Reid F, Lobo DN, Williams RN, Rowlands BJ, Allison SP. (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. *Clin Sci Lond* 2003; **104**: 17–24
- 24 Wilkes NJ, Woolf R, Mutch M, et al. The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid–base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. *Anesth Analg* 2001; **93**: 811–6
- 25 Khajavi MR, Etezadi F, Moharari RS, et al. Effects of normal saline vs. lactated ringer's during renal transplantation. *Ren Fail* 2008; **30**: 535–9
- 26 Stephens RC, Mythen MG. Saline-based fluids can cause a significant acidosis that may be clinically relevant. *Crit Care Med* 2000; **28**: 3375–7
- 27 Van der Linden P, Ickx BR. The effects of colloid solutions on hemostasis. *Can J Anaesth* 2006; **53**: S30–9
- 28 Rehm M, Orth VH, Kreimeier U, et al. Changes in blood volume during acute normovolemic hemodilution with 5% albumin or 6% hydroxyethylstarch and intraoperative retransfusion. *Anaesthesist* 2001; **50**: 569–79
- 29 Lobo DN, Stanga Z, Aloysius MM, et al. Effect of volume loading with 1 liter intravenous infusions of 0.9% saline, 4% succinylated gelatine (Gelofusine) and 6% hydroxyethyl starch (Voluven) on blood volume and endocrine responses: a randomized, three-way crossover study in healthy volunteers. *Crit Care Med* 2010; **38**: 464–70
- 30 Kamp-Jensen M, Olesen KL, Bach V, Schutten HJ, Engquist A. 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. *Br J Anaesth* 1990; **64**: 606–10
- 31 Hartog CS, Kohl M, Reinhart K. A systematic review of third-generation hydroxyethyl starch (HES 130/0.4) in resuscitation: safety not adequately addressed. *Anesth Analg* 2011; **112**: 635–45
- 32 Trof RJ, Sukul SP, Twisk JW, Girbes AR, Groeneveld AB. Greater cardiac response of colloid than saline fluid loading in septic and non-septic critically ill patients with clinical hypovolaemia. *Intensive Care Med* 2010; **36**: 697–701
- 33 James MF, Michell WL, Joubert IA, Nicol AJ, Navsaria PH, Gillespie RS. Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma). *Br J Anaesth* 2011; **107**: 693–702
- 34 Jackson R, Reid JA, Thorburn J. Volume preloading is not essential to prevent spinal-induced hypotension at Caesarean section. *Br J Anaesth* 1995; **75**: 262–5
- 35 Norberg A, Hahn RG, Li H, et al. Population volume kinetics predicts retention of 0.9% saline infused in awake and isoflurane-anesthetized volunteers. *Anesthesiology* 2007; **107**: 24–32
- 36 Jacob M, Chappell D, Conzen P, Finsterer U, Rehm M. Blood volume is normal after pre-operative overnight fasting. *Acta Anaesthesiol Scand* 2008; **52**: 522–9
- 37 Brady M, Kinn S, Stuart P. Preoperative fasting for adults to prevent perioperative complications. *Cochrane Database Syst Rev* 2003: CD004423
- 38 Lobo DN, MacAfee DA, Allison SP. How perioperative fluid balance influences postoperative outcomes. *Best Pract Res Clin Anaesthesiol* 2006; **20**: 439–55
- 39 Contant CM, Hop WC, van't Sant HP, et al. Mechanical bowel preparation for elective colorectal surgery: a multicentre randomised trial. *Lancet* 2007; **370**: 2112–7
- 40 Shires T, Williams J, Brown F. Acute change in extracellular fluids associated with major surgical procedures. *Ann Surg* 1961; **154**: 803–10
- 41 Lowell JA, Schifferdecker C, Driscoll DF, Benotti PN, Bistran BR. Postoperative fluid overload: not a benign problem. *Crit Care Med* 1990; **18**: 728–33
- 42 Holte K, Jensen P, Kehlet H. Physiologic effects of intravenous fluid administration in healthy volunteers. *Anesth Analg* 2003; **96**: 1504–9
- 43 Brandstrup B, Svendsen C, Engquist A. Hemorrhage and operation cause a contraction of the extracellular space needing replacement—evidence and implications? A systematic review. *Surgery* 2006; **139**: 419–32
- 44 Lamke LO, Nilsson GE, Reithner HL. Water loss by evaporation from the abdominal cavity during surgery. *Acta Chir Scand* 1977; **143**: 279–84
- 45 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. *Ann Surg* 2003; **238**: 641–8
- 46 Bundgaard-Nielsen M, Secher NH, Kehlet H. 'Liberal' vs. 'restrictive' perioperative fluid therapy—a critical assessment of the evidence. *Acta Anaesthesiol Scand* 2009; **53**: 843–51
- 47 MacKay G, Fearson K, McConnachie A, Serpell MG, Molloy RG, O'Dwyer PJ. Randomized clinical trial of the effect of postoperative intravenous fluid restriction on recovery after elective colorectal surgery. *Br J Surg* 2006; **93**: 1469–74
- 48 Holte K, Foss NB, Anderson J, et al. Liberal or restrictive fluid administration in fast-track colonic surgery: a randomized, double-blind study. *Br J Anaesth* 2007; **99**: 500–8
- 49 Holte K, Kristensen BB, Valentiner L, Foss NB, Husted H, Kehlet H. Liberal versus restrictive fluid management in knee arthroplasty: a randomized, double-blind study. *Anesth Analg* 2007; **105**: 465–74
- 50 Maharaj CH, Kallam SR, Malik A, Hassett P, Grady D, Laffey JG. Preoperative intravenous fluid therapy decreases postoperative nausea and pain in high risk patients. *Anesth Analg* 2005; **100**: 675–82
- 51 Lambert KG, Wakim JH, Lambert NE. Preoperative fluid bolus and reduction of postoperative nausea and vomiting in patients undergoing laparoscopic gynecologic surgery. *AANA J* 2009; **77**: 110–4
- 52 Holte K, Klarskov B, Christensen DS, et al. Liberal versus restrictive fluid administration to improve recovery after laparoscopic

- cholecystectomy: a randomized, double-blind study. *Ann Surg* 2004; **240**: 892–9
- 53 Brandstrup B. Fluid therapy for the surgical patient. *Best Pract Res Clin Anaesthesiol* 2006; **20**: 265–83
- 54 Nisanevich V, Felsenstein I, Almogy G, Weissman C, Einav S, Matot I. Effect of intraoperative fluid management on outcome after intraabdominal surgery. *Anesthesiology* 2005; **103**: 25–32
- 55 Kabon B, Akca O, Taguchi A, et al. Supplemental intravenous crystalloid administration does not reduce the risk of surgical wound infection. *Anesth Analg* 2005; **101**: 1546–53
- 56 Tatara T, Nagao Y, Tashiro C. The effect of duration of surgery on fluid balance during abdominal surgery: a mathematical model. *Anesth Analg* 2009; **109**: 211–6
- 57 Hamilton MA. Perioperative fluid management: progress despite lingering controversies. *Cleve Clin J Med* 2009; **76**: S28–31
- 58 Hamilton-Davies C, Mythen MG, Salmon JB, Jacobson D, Shukla A, Webb AR. Comparison of commonly used clinical indicators of hypovolaemia with gastrointestinal tonometry. *Intensive Care Med* 1997; **23**: 276–81
- 59 Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest* 2008; **134**: 172–8
- 60 Miller T, Gan TJ. Goal-directed fluid therapy. In: Hahn RG, ed. *Clinical Fluid Therapy in the Perioperative Setting*, vol. 11. Cambridge: Cambridge University Press, 2011; 91–9
- 61 Shoemaker WC, Appel PL, Kram HB, et al. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest* 1988; **94**: 1176–86
- 62 Cecconi M, Fasano N, Langiano N, et al. Goal-directed haemodynamic therapy during elective total hip arthroplasty under regional anaesthesia. *Crit Care* 2011; **15**: R132
- 63 Van der Linden PJ, Dierick A, Wilmin S, Bellens B, De Hert SG. A randomized controlled trial comparing an intraoperative goal-directed strategy with routine clinical practice in patients undergoing peripheral arterial surgery. *Eur J Anaesthesiol* 2010; **27**: 788–93
- 64 Hamilton MA, Cecconi M, Rhodes A. A systematic review and meta-analysis on the use of preemptive haemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. *Anesth Analg* 2011; **112**: 1392–402
- 65 Lobo SM, Ronchi LS, Oliveira NE, et al. Restrictive strategy of intraoperative fluid maintenance during optimization of oxygen delivery decreases major complications after high risk surgery. *Crit Care* 2011; **15**: R226
- 66 Bundgaard-Nielsen M, Holte K, Secher NH, Kehlet H. Monitoring of peri-operative fluid administration by individualized goal-directed therapy. *Acta Anaesthesiol Scand* 2007; **51**: 331–40
- 67 Kuper M, Gold SJ, Callow C, et al. Intraoperative fluid management guided by oesophageal Doppler monitoring. *Br Med J* 2011; **342**: d3016
- 68 Bundgaard-Nielsen M, Ruhnau B, Secher NH, Kehlet H. Flow-related techniques for preoperative goal-directed fluid optimization. *Br J Anaesth* 2007; **98**: 38–44
- 69 Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. *Arch Surg* 1995; **130**: 423–9
- 70 Sinclair S, James S, Singer M. Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. *Br Med J* 1997; **315**: 909–12
- 71 Venn R, Steele A, Richardson P, Poloniecki J, Grounds M, Newman P. Randomized controlled trial to investigate influence of the fluid challenge on duration of hospital stay and perioperative morbidity in patients with hip fractures. *Br J Anaesth* 2002; **88**: 65–71
- 72 Abbas SM, Hill AG. Systematic review of the literature for the use of oesophageal Doppler monitor for fluid replacement in major abdominal surgery. *Anaesthesia* 2008; **63**: 44–51
- 73 Walsh SR, Tang T, Bass S, Gaunt ME. Doppler-guided intra-operative fluid management during major abdominal surgery: systematic review and meta-analysis. *Int J Clin Pract* 2008; **62**: 466–70
- 74 National Institute for Health and Clinical Excellence (NICE). Available from <http://guidance.nice.org.uk/MTG3> (accessed 20 December 2011)
- 75 Powell-Tuck J, Gosling P, Lobo DN, et al. *British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients (GIFTASUP)*, 2011. Available from http://www.bapen.org.uk/pdfs/bapen_pubs/giftasup.pdf (accessed 20 December 2011)
- 76 *Decision Memo for Ultrasound Diagnostic Procedures (CAG-00309R)*. 2007. Available from <http://www.cms.gov> (accessed 20 December 2011)
- 77 Lassen K, Soop M, Nygren J, et al. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. *Arch Surg* 2009; **144**: 961–9
- 78 Morris C, Rogerson D. What is the optimal type of fluid to be used for peri-operative fluid optimisation directed by oesophageal Doppler monitoring? *Anaesthesia* 2011; **66**: 819–27
- 79 Senagore AJ, Emery T, Luchefeld M, Kim D, Dujovny N, Hoedema R. Fluid management for laparoscopic colectomy: a prospective, randomized assessment of goal-directed administration of balanced salt solution or hetastarch coupled with an enhanced recovery program. *Dis Colon Rectum* 2009; **52**: 1935–40
- 80 Srinivasa S, Taylor MHG, Sammour T, Kahokehr AA, Hill AG. Oesophageal Doppler-guided fluid administration in colorectal surgery: critical appraisal of published clinical trials. *Acta Anaesthesiol Scand* 2011; **55**: 4–13
- 81 Challand C, Struthers R, Sneyd JR, et al. Randomised controlled trial of intraoperative goal-directed fluid therapy in aerobically fit and unfit patients having major colorectal surgery. *Br J Anaesth* 2012; **108**: 53–62