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Pathophysiology and clinical implications of perioperative fluid excess

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The practice of perioperative fluid therapy is variable, ranging from 'high volume' to 'dry' regimen. A review of the data on the effect of 'high volume' perioperative fluid therapy suggests that the resulting overhydration may have deleterious effects on cardiac and pulmonary function, and on recovery of gastrointestinal motility (postoperative ileus), tissue oxygenation, wound healing and coagulation. These observations call for randomized studies of the effects of 'high' *vs* 'low' volume replacement therapy on postoperative morbidity, in order to establish evidence-based guidelines for perioperative fluid management.

Perioperative fluid replacement has been, and still is, the focus of much debate. This debate has primarily focused on the various types of fluid components available for replacement therapy, and not on the actual amount of fluid administered.

The principles of perioperative fluid therapy were fostered in the late 1950s and early 1960s. Recommendations for restricted fluid regimen came primarily from Francis Moore,[85] arguing that the net effect of the obligatory metabolic–endocrine response to trauma, which is conservation of water and sodium, implied restriction in fluid delivery. In contrast, Tom Shires[129] postulated a decrease in extracellular volume after surgery, due to internal redistribution of fluids, the 'third space' losses, and advocated replacement of these losses by additional fluid infusion. These considerations were supported by studies during the Korean War, where large amounts of fluid were administered in trauma patients with improved survival, thereby also influencing the recommendations for elective surgery.[6] The concept of resuscitation in order to achieve supranormal circulatory function was developed in the 1970s and 1980s by Shoemaker,[130] and obtained primarily by the use of fluid infusions and inotropes. Clinical practice has largely been influenced by Shires' recommendations and it has not been uncommon to see very large amounts of fluid administered in elective surgical procedures, way in excess of the actual losses. This is especially the case in major aortic or abdominal surgery, where 4–6 litres or more of intraoperative fluid substitution (apart from replacement of blood losses) have been given,[22 35 66 134] or in peripheral vascular surgery with more than 6 litres of fluid administered within surgery and the first 24 h after surgery, despite a minimal blood loss.[19] Up to 4 litres of fluid have been administered within the first 24 h in patients undergoing laparoscopic cholecystectomy.[36] In contrast, in thoracic surgery, relatively 'dry' regimen have been considered to be beneficial, due to the association between the amount of administered fluid and the development of post-pneumonectomy pulmonary oedema.[52 133 149]

Several issues in perioperative management may account for the administration of excessive amounts of fluid, including concern about preoperative fluid deficits (dehydration, primarily derived from prolonged preoperative fasting and bowel preparation), attempts to support the circulation and cardiac function after general and regional anaesthesia, attempts to control the circulation postoperatively, administration of crystalloid or colloid to avoid blood transfusion, preservation of urine output and preservation of a high CVP from fluid infusion.

Administration of excess fluid may cause several problems after surgery. The resulting increased demands on cardiac function, due to an excessive shift to the right on the Starling myocardial performance curve, may potentially increase postoperative cardiac morbidity. Fluid accumulation in the lungs may predispose patients to pneumonia and respiratory failure. The excretory demands of the kidney are increased, and the resulting diuresis may lead to urinary

Table 1 Hormonal responses to surgery and fluid overload

Hormone	Response to surgery (Reference numbers)	Response to overload	Effect on fluid distribution
Aldosterone	Increase (27, 143)	Decrease (142)	Sodium and fluid retention; potassium excretion
Antidiuretic hormone	Increase (27, 143)	Decrease (48)	Water retention
Renin–angiotensin II	Increase (27, 143)	Decrease (2–4, 94, 142)	Sodium and fluid retention; potassium excretion
Atrial natriuretic peptide	Increase or no change (59, 62, 63)	Increase (54, 68, 119, 146)	Diuretic; natriuretic

retention mediated by the inhibitory effects of anaesthetics and analgesics on bladder function. Gastrointestinal motility may be inhibited, prolonging postoperative ileus. Excess fluid may decrease tissue oxygenation with implications for wound (anastomotic) healing. Finally, coagulation may be enhanced with crystalloids, which may predispose patients to postoperative thrombosis.

In this review we summarize the pathophysiology of perioperative fluid excess, and review the effects of it on organ function and the potential clinical implications. We discuss the aspects of fluid management in regional anaesthesia, and the implications of immobilization on fluid homeostasis. We focus on perioperative fluid therapy in elective surgical procedures. We do not intend to present recommendations on fluid replacement strategies, or to discuss the various components available for fluid replacement or the current methods of monitoring fluid balance. Furthermore, we do not intend to discuss the treatment options for hypovolaemia or the use of i.v. fluids in critically ill patients.

Surgical stress and fluid responses

Water makes up 60% of total body weight, one third of it being extracellular fluid volume (ECV) (interstitial fluid and plasma), and two thirds being intracellular volume. Transportation of fluid between the body compartments is regulated by the Starling equilibrium, the decisive variables being differences in hydrostatic and colloid osmotic pressure, and specific permeability coefficients. In response to surgery, serum colloid osmotic pressure is decreased,[64 125] which is primarily caused by increased capillary permeability, resulting in fluid shifts from the vascular bed to the interstitial fluid.[60 125] Dilution secondary to crystalloid infusions may also contribute.[71] In addition, as a physiological response to a decrease in intravascular pressure, fluid movement from the extravascular to the intravascular space occurs, as demonstrated in a human volunteer study where experimental hypovolaemia led to fluid movements from tissue to blood.[74]

Changes in ECV after surgery have been much debated, and fluid replacement today is greatly influenced by Shires,[127 129] who postulated a decrease in *functional* (i.e. exchangeable) ECV after elective surgical procedures and haemorrhagic shock. According to Shires, surgical trauma *per se* (without administration of fluids) led to a decrease in functional ECV, which was proportional to the degree of surgical trauma.[129] Shires primarily explained the decrease in functional ECV by sequestration of fluids within the traumatized area or expansion of the intracellular volume, and therefore advocated replacement of these losses with additional saline infusions.[110 128 129] However, these observations have been contradicted by several other investigators reporting unchanged,[40 65 91 138] or even increased,[21 112] ECV in postoperative patients, and studies in major surgery suggest that ECV expansion may correlate with intraoperative fluid administration.[93 112] Thus, a positive fluid balance of 3 litres was associated with unchanged ECV, but a smaller or larger fluid excess with a decrease or increase in ECV, respectively.[93] In other studies, intracellular volume has been found to be decreased after surgery (intracellular dehydration).[31] Difficulty in obtaining accurate measurements of the fluid phases is generally recognized,[86] however, and may relate to the use of isotopes with different volumes of distribution, different equilibrium times and general changes in equilibrium times and distribution volumes as a consequence of the surgical trauma.

Therefore, despite 30 yr of research, perioperative ECV changes have not been clarified. However, the present data suggest that the magnitude of ECV decrease suggested by Shires may not be accurate, partly because the type of surgery, anaesthesia and perioperative fluid management were not standardized. Further studies are required to assess ECV changes after surgery with standardized regimen.

Surgery elicits a stress response of combined endocrine and inflammatory origin.[27 143] Several of the hormones involved in this response may exert a potentially profound influence on the distribution of body fluids (Table 1). Generally, the endocrine response to surgical trauma leads to conservation of sodium and water and to excretion of potassium, the principal mediators being antidiuretic hormone (ADH), aldosterone and the renin–angiotensin II system.[27 143] The increased ADH secretion leads to enhanced water reabsorption in the kidney, resulting in a postoperative decrease in diuresis and a decrease in plasma concentrations of sodium. The increased secretion of aldosterone and renin leads to conservation of sodium and excretion of potassium. Several other mediators, enhanced by the surgical stress, may influence the distribution of fluid. Thus, increased cortisol secretion, an obligatory stress response, may be of major importance in the control fluid

homeostasis, primarily through permissive actions to maintain capillary integrity.[117] In addition, the cortisol-induced inhibition of excessive inflammatory activity response to trauma may reduce postoperative fluid shifts.[117] Atrial natriuretic peptide (ANP) secretion in response to surgery is unclear because ANP secretion may be increased in older patients, in contrast to unchanged ANP levels in younger patients.[59 62 63] ANP may induce natriuresis, diuresis and inhibition of aldosterone and ADH secretion.[90] Furthermore, inflammatory mediators, like IL-6, TNF, substance-P and bradykinin may act as vasodilators and increase capillary permeability. The release of these inflammatory mediators is proportional to the magnitude of the surgical trauma.[58] The hormonal release in response to surgical trauma therefore generally induces a shift toward water and sodium retention, while the excretion of potassium is increased, paralleling the increase in catabolism.

Studies in healthy volunteers make it possible to investigate the individual factors of importance in perioperative fluid balance, independently of the surgical trauma; the surgically induced factors, such as increased capillary permeability, are eliminated when studying volunteers. In order to investigate the effects of the stress responses seen after surgery *per se*, continuous infusions (>2 days) of cortisol/hydrocortisone, glucagon and epinephrine have, in three studies in healthy volunteers, been found to decrease sodium excretion and increase potassium excretion.[10 11 140] Furthermore, in two of these studies a weight gain of approximately 0.4 and 1.7 kg, respectively, was seen.[11 140] These findings were not modified by the concomitant infusion of an inflammatory agent (ethiocholanolone),[140] despite an increased acute phase protein response. These results demonstrate that activation of the stress response leads to fluid retention.

In contrast, several of the stress responses to injury may be influenced by fluid volume expansion *per se.* Increased capillary permeability leading to increased filtration of plasma proteins was seen after infusion of Dextran 1000 ml or 360 ml of albumin in healthy volunteers.[96] The inhibition of aldosterone secretion with fluid infusions is well established, both in healthy volunteers and surgical patients.[142] Attenuation of ADH secretion seems only to occur with high volume fluid infusions of about 50 ml min^{-1},[48] while lower infusion volumes of 15 ml min^{-1} [12] or 15 ml kg^{-1} h^{-1} [132] did not attenuate it. ANP secretion is increased after saline infusion in healthy volunteers,[54 68 119 146] but the response is transient and occurs within and immediately after the infusion. The renin–angiotensin II secretion is inhibited with fluid administration, and evidence suggests that the renin–angiotensin II system is of major importance in the excretion of a fluid overload.[2–4 29 94 142] However, there is no systematic evaluation of ANP and renin responses to fluid regimen in surgical procedures.

A large fluid volume therefore influences several of the hormonal responses to injury in surgical patients (decrease in ADH, decrease in aldosterone), while the effect of fluid administration on other hormones known to be increased postoperatively (renin and ANP) has only been systematically evaluated in healthy volunteers. Thus, the effects of perioperative fluid administration on the stress responses to surgery are unclear and need to be evaluated in clinical studies comparing high *vs* low fluid regimen.

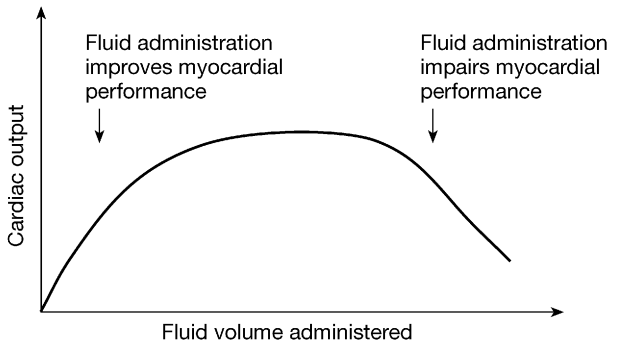

Fig 1 Effects of perioperative fluid therapy on the Starling myocardial performance curve.

Organ dysfunction and postoperative complications

Cardiac function and morbidity

The physiological relationship between cardiac filling and cardiac output is described in Starling's myocardial performance curve (Fig. 1). The curve describes the functional consequences of alterations in preload on cardiac output, and is the rationale behind improvement of cardiac output by volume administration. Until a certain point, volume expansion leads to increased cardiac output due to increased end-diastolic ventricular filling. Beyond that point, increased end-diastolic volume will lead to a decrease in cardiac output due to depression of ventricular function. Measurements of cardiac responses (primarily cardiac output) in response to a fluid load have been used to define the optimal ventricular filling pressures (evaluated by pulmonary artery catheter measurements).[15 77 141] However, although increases in end-diastolic filling pressures may increase cardiac output, the effects on other aspects of ventricular function, such as the ejection fraction and end-systolic pressure, may occur at different filling pressures.[76] This makes determination of the effect of the optimal end-diastolic filling pressure on overall cardiac function difficult by intravascular catheter measurements. In one study during cardiac surgery, plasma volume expansion to achieve maximal ventricular stroke volume assessed by oesophageal Doppler measurements (on average 900 ml crystalloid and 1400 ml colloid) led to a significantly better perfusion of the gastrointestinal mucosa and a significant decrease in major postoperative complications (major infections, stroke, paralytic ileus, respiratory failure and death).[89] Furthermore, in a

randomized study in 40 patients undergoing surgery for hip fracture, intraoperative fluid infusion to maximize ventricular stroke volume (on average 750 ml of colloid infusion) led to improvements in postoperative mobilization and hospital stay.[131] In these studies, however, patients did not receive excessive fluid, but were adequately resuscitated, thus optimizing their position on the Starling curve. In a prospective study of 4059 patients undergoing major elective non-cardiac surgery, patients who underwent perioperative right-heart catheterization had a threefold increase in the incidence of major postoperative cardiac events (ischaemic events, arrhythmia or heart failure) compared with patients who were not catheterized (15.4 *vs* 3.6%).[104] The catheterized patients were also given more fluids (net fluid balance of 3.2 *vs* 2.0 litres), and the authors suggested that the adverse outcome was due, at least in part, to excessive fluid administration. However, since fluid administration was determined by right-heart catheterization and not investigated *per se*, these results are inconclusive with regard to the potentially deleterious effects of fluid overload.

Fluid loading to optimize cardiac function should therefore be guided by the Starling curve, and may have beneficial effects on postoperative organ function. Theoretically, perioperative infusions of excessive amounts of fluid may increase cardiovascular demands and morbidity. However, this has not been specifically investigated in randomized studies comparing low *vs* high fluid regimen.

Pulmonary function and complications

Removal of excess fluid from the alveolar space is also driven by active sodium transport, and not only, as previously believed, by differences in hydrostatic and colloid osmotic pressures.[79] The sodium channels involved may potentially be upregulated by catecholamines and glucocorticoids as well as by proinflammatory cytokines, all of which are increased in response to surgery,[79] and modified by fluid administration as already discussed. This may account for the conflicting evidence from previous studies examining the relations between fluid administration and pulmonary oedema.[52] In response to an i.v. saline load of 22 ml kg^{-1} in healthy volunteers, functional residual capacity decreased by 10% and diffusing capacity by 6%, both of which had not returned to normal 40 min after the infusion (later measurements were not made).[45] In another study in five volunteers, infusion of 1 litre of isotonic saline led to small decreases in total lung capacity (about 0.25 litres) and forced vital capacity (about 0.1 litres), which returned to normal after 1 h. Infusion of 2 litres of normal saline led to a similar decrease in the same variables; the effects were still present 1 h after the infusion, but recovered after subsequent furosemide administration.[23]

The incidence of pulmonary oedema after lung surgery may be as high as 12–15%.[52] The pathogenesis is unclear, but impaired lymphatic drainage, the extent of surgical injury and one-lung ventilation may be of importance. The volume of fluids administered during the perioperative course has been found to correlate with the development of post-pneumonectomy pulmonary oedema.[133 137 149] In retrospective studies, a 24-h fluid replacement of >3 litres,[97] and intra-operative fluid load of 2000 ml or more,[95] were predictive factors for the development of post-pneumonectomy pulmonary oedema. However, in some retrospective studies, post-pneumonectomy pulmonary oedema was not related to the volume of administered fluids.[135 139] These findings have not been investigated in randomized clinical trials comparing high *vs* low fluid regimen.

In non-thoracic surgery, excessive fluid administration may also result in adverse respiratory function. In 13 patients, the development of lung oedema after various elective surgical procedures correlated with a net fluid retention exceeding 67 ml $kg^{-1}day^{-1}$.[5] In a randomized study between general and regional anaesthesia in peripheral vascular surgery with minimal blood loss, patients received more than 6 litres of crystalloid infusion within 24 h after surgery.[19] Despite the low surgical stress, the overall pulmonary morbidity was exceptionally high, since 10% of the patients developed respiratory failure.[19]

Renal function and urinary retention

Since the kidneys are responsible for excretion of the majority of administered fluids, renal functional demands are increased in a state of fluid overload. In addition, the hormonal responses after injury may decrease water and sodium excretion, primarily due to the enhanced secretion of ADH, aldosterone and renin.[27] The glomerular filtration rate (GFR) was significantly increased with administration of 210–300 ml m^{-2} h^{-1} of a balanced salt solution compared with 75–200 ml m^{-2} h^{-1} during surgery.[47] In 53 patients undergoing major vascular surgery, GFR was also found to increase after surgery, with cumulated fluid balances of 2.2–6 litres, explained by an increase in ECV, renal plasma flow or both.[92] On the other hand, several studies in healthy volunteers have demonstrated that excretion of an acute saline overload (22 ml kg^{-1}) takes approximately 2 days.[28–30] Of 20 burn patients receiving an overload of 3–7 litres, only ten had excreted the overload within 1 week.[39] The prolonged fluid elimination has been found to correlate with elevated levels of urodilatin (an ANP-related polypeptide), and decreased levels of renin in healthy volunteers.[28 29]

General anaesthesia may exert an inhibitory effect on renal haemodynamics and function, reflected in the depression of GFR, urinary volume and sodium excretion.[26] However, the relationship between haemodynamics and renal function is not clear. Thus, in 987 patients undergoing total hip replacement with hypotensive epidural anaesthesia, in which intraoperative fluid averaged 1200 ml, renal dysfunction was not present.[124]

Without fluid load, urine output is negligible under general anaesthesia.[25] Consequently, fluid is generally administered to maintain a higher urine output, based upon a fear that renal failure may develop if urine flow is low.[126] However, there is no evidence of an association between low urine output *per se* and the development of renal failure (providing hypovolaemia is not present), as demonstrated in 137 consecutive patients undergoing abdominal aortic revascularization, where intraoperative urine output did not predict postoperative renal function.[1] Optimal preoperative fluid loading using the Starling curve (left side of the Starling curve, Fig. 1) has not been proven to prevent postoperative renal insufficiency.[108] In 100 critically ill patients, development of oliguria was not related to the amounts of fluid administered,[147] and it occurred in the presence of normal blood urea and creatinine. In 24 patients undergoing major neck surgery and randomized to 'generous' or 'restricted' fluid regimen, intraoperative urine output in the 'restricted' fluid group was 0.4 ml kg^{-1} h^{-1} compared with 1.33 ml kg^{-1} h^{-1} in the 'generous' fluid group.[106] Nevertheless, postoperative renal function remained normal in both groups. In 14 adult recipients of living-donor kidneys, who were randomly assigned to high fluid replacement (urine output plus 30 ml h^{-1}) or low fluid replacement (constant 125 ml h^{-1}), urine output was significantly higher in the high-replacement group, and urine osmolality was significantly higher in the low-replacement group.[43] However, no differences were found between groups in 48-h fluid balance or GFR.

Intraoperative oliguria due to moderate fluid restriction is not therefore detrimental to renal outcome. Excretion of a fluid excess in the range of 1.5–2 litres may take more than 2 days in healthy volunteers and even more in surgical patients, indicating that the functional demands of the kidney may be increased for up to a week after surgery, depending on the nature and amount of fluid administered and the magnitude of surgery. However, the role of fluid excess in postoperative renal morbidity is unknown.

Urinary retention is commonly seen after surgery, and is a recognized complication of spinal and epidural local anaesthetic techniques, as well as postoperative opioid analgesia, due to their inhibitory effects on bladder muscle function.[7 101] A fluid overload may therefore increase the risk of postoperative urinary retention. However, urinary retention may occur also in the absence of overload, as in patients with prostate hypertrophy. Compared with other surgery, patients having anal or hernia surgery are at greater risk of developing postoperative urinary retention.[98] Thus, restriction of perioperative fluids in anorectal surgery reduces the risk of urinary retention.[8 16 100 120] In hernia surgery, perioperative administration of >1200 ml of fluid[103] or fluid infusions of >750 ml[46] was significantly associated with an increase in the incidence of urinary retention. In a randomized study in 133 hernia patients, administration of <500 ml fluid compared with 1300 ml, led to a lower (although non-significant) incidence of urinary retention.[61] However, a randomized study of intraoperative administration of 2 ml kg^{-1} *vs* 10 ml kg^{-1} of i.v. fluid to low-risk outpatients (no hernia or anal surgery, and no history of urinary retention in patients with regional anaesthesia),[98] found no difference in urinary retention between the groups. Retrospective studies in patients undergoing hysterectomy,[99] appendectomy,[101] and cholecystectomy,[102] did not find significant correlations between fluid administration and postoperative urinary retention.

Abdominal compartment syndrome and gastrointestinal function

The abdominal compartment syndrome (ACS) is defined as a postoperative or post-traumatic elevation in intra-abdominal pressure leading to adverse physiological effects, most commonly respiratory and renal failure.[14] Development of ACS may be associated with the administration of large amounts of fluid. Thus, the crystalloid volume administered to six patients with ACS was found to be 19 litres in <24 h.[80] Infusion of a volume equal to 15–20% of the body weight led to elevated intra-abdominal pressure and decreased respiratory function in an experimental study in pigs.[88] In addition, increased abdominal pressure has been found to stimulate ADH release, thus promoting further fluid retention.[67]

Fluid overload may lead to oedema of the gut, possibly contributing to enteric nutritional intolerance, prolonged ileus and translocation of endotoxin or bacteria, with potentially deleterious implications such as sepsis and multiorgan failure.[109 144] However, evidence from a study in 18 patients undergoing gastrointestinal surgery suggests that infusions of crystalloids as opposed to colloids may predispose them to the development of intestinal oedema.[107] These patients randomly received either lactated Ringer's solution (mean volume infused, 3850 ml), 10% hydroxyethyl starch (mean volume infused, 1358 ml), or 20% human albumin (mean volume infused, 463 ml), to maintain central venous pressure at the preoperative level. Colloid osmotic pressure was unchanged in the colloid groups, and intestinal oedema was found only in the group receiving crystalloids. Results from a study in 20 patients undergoing colonic surgery and randomized to a 'standard' postoperative fluid regimen (minimum of 3 litres of water and 154 mmol sodium day^{-1}), or a restricted postoperative fluid regimen (maximum of 2 litres of water and 77 mmol sodium day^{-1}), found a significant reduction in postoperative ileus with fluid restriction (4.0 *vs* 6.5 days).[70] Furthermore, postoperative hospital stay decreased from a median of 9–6 days in the patients with the restricted postoperative fluid regimen. Lowered concentrations of plasma proteins may follow administration of 2 litres of saline even in the absence of surgery,[71 87] and in experimental studies hypoproteinaemia was associated with decreased gastrointestinal motility.[41] In a prospective study in vascular surgery, an albumin concentration of <35 g $litre^{-1}$ did not

correlate with increased duration of postoperative ileus, compared with patients where the concentration of albumin was maintained above 35 g litre^{-1} with albumin infusions.[145] In experimentally performed gastrointestinal anastomoses in rabbits, administration of 5 ml kg^{-1} h^{-1} of isotonic saline during surgery followed by 200 ml in the first 48 h after surgery (compared with no fluid administration), led to a significant increase in tissue weight at the anastomotic site, persisting for 5 days after surgery.[17] The resulting impairment in tissue oxygenation may potentially have deleterious effects on anastomotic healing. The available data from these studies are preliminary and need to be addressed in future, randomized, large-scale clinical trials.

Oedema, wound healing and tissue hypoxaemia

Oedema is a clinical sign of subcutaneous fluid accumulation, which inevitably leads to impaired oxygen diffusion and decreased tissue oxygen tension, due to increased endothelial cellular distance. The relation between serum colloid osmotic pressure and interstitial oedema is not directly proportional, since the oedema becomes progressively greater as serum colloid pressure decreases.[73] Tissue oxygen tension in experimental wounds, measured by aspiration of fluid from an implanted mesh cylinder, was progressively lowered with increasing amounts of fluid administered, when 2.5, 5 or 10 ml kg^{-1} of isotonic saline solution was administered to rabbits.[44] Furthermore, when 10 ml kg^{-1} of isotone saline was administered, it took 3.5 days for tissue oxygen tension to recover to control values. In a randomized study in 42 patients scheduled for major abdominal surgery, 24 h of intra- and postoperative administration of 3 litres of hydroxyethyl starch and 3 litres of Ringer's solution was compared with 11.7 litres of Ringer's solution. There was a resulting significant decrease in tissue oxygen tension (measured via a catheter inserted in the deltoid muscle) in the crystalloid group.[66] However, in a randomized trial in major abdominal surgery, replacement of fluid according to measurements of subcutaneous oxygen tension (via a silicone catheter inserted subcutaneously in the upper arm) rather than by clinical criteria (5.7 *vs* 4.6 litres of crystalloid administered on the day of surgery), resulted in improved collagen accumulation in wounds.[42] Since wound healing may be inhibited by tissue hypoxaemia,[51] the risk of decreased oxygen tension secondary to interstitial fluid accumulation should be further evaluated in studies of low *vs* high fluid administration.

Coagulation

Impaired coagulation is a recognized complication of the use of synthetic colloids for volume replacement.[38] In contrast, infusions of crystalloids have been demonstrated to induce a hypercoagulable state both *in vitro* and *in vivo*,[114 115] which is not seen with some colloid infusions.[56] The mechanisms behind the hypercoagulable effects of crystalloids are unknown, but decreased activity of anticoagulatory factors may be of importance.[116] These findings have been confirmed in 60 patients undergoing major abdominal surgery, randomized to receive i.v. fluids during or after the operation (i.v. Hartmann's solution 1 litre h^{-1} of operation and dextrose-saline 2–3 litres 24 h^{-1} for 2 days), or receiving no i.v. fluids during or after surgery.[50] The incidence of postoperative deep venous thrombosis was significantly higher in the patients receiving fluids (30%), compared with only 7% in the patients who did not receive i.v. fluid. Furthermore, the patients receiving fluids became significantly more haemodilute and hypercoagulable compared with those who did not. However, the results from this study are difficult to interpret, since administration of no intraoperative fluids in abdominal surgery is not compatible with common practice.

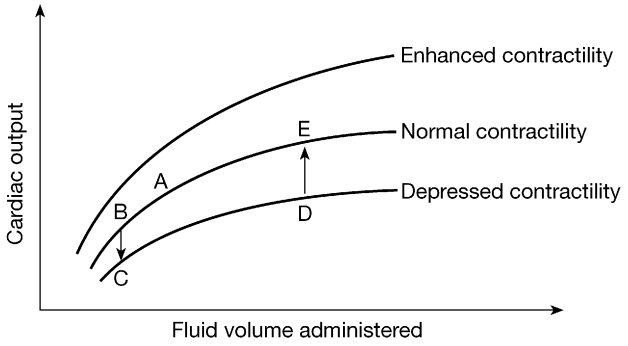

Fig 2 Relationship between cardiac output and fluid administration. General anaesthesia or extensive epidural/spinal anaesthesia result in venodilatation and cardiac depression. Venodilatation leads to a reduction in preload depicted by transfer from Point A (baseline) to B on the normal contractility curve. Cardiac depression results in a fall to a depressed contractility curve (Point C). Restoration of cardiac output with fluid alone is depicted by the line from Point C to D. With resolution of epidural anaesthesia or emergence from general anaesthesia, the patient is apt to be hyperdynamic and fluid overloaded (Point E). By contrast, if extensive epidural/spinal anaesthesia is managed with vasopressors, restoration of contractility (Point C to B) and venous tone (Point B to A) can be achieved without fluid loading.

Specific considerations

Regional anaesthesia

In theory, regional anaesthesia should be followed by decreased requirements for intraoperative fluid administration due to a decrease in perioperative blood loss.[57 111] In a retrospective study of mortality during a 10-yr period of hip and knee replacement surgery, mortality decreased from 0.4 to 0.1% concomitant with extensive changes in anaesthetic technique, including a shift from general to epidural anaesthesia.[121] In addition, intraoperative fluid administration was reduced from 3108 to 1563 ml during that 10-yr period. Although cardiac output may be increased by

increasing preload (Fig. 2), it may also be increased by administering sympathomimetics, leading to improved myocardial contractility with unchanged preload. Regional anaesthesia to the upper thoracic dermatomes is associated with a significant reduction in preload and an impairment of cardiac sympathetic drive, resulting in a reduction in cardiac output and hypotension.[123] A substantial volume of fluid is required to augment cardiac output in this setting,[148] whereas vasopressors with α and β activity, such as ephedrine,[122] dopamine[72] or epinephrine, can restore cardiac output without excessive volume administration. Low levels of spinal or epidural anaesthesia (T8 or below) usually result in minimal circulatory changes, as the compensatory vasoconstriction in the upper part of the body is sufficient to offset the dilatation in the lower extremities.[69] In this setting, excessive fluid is usually not needed to preserve haemodynamic stability. Thus, fluid administration prior to spinal or epidural anaesthesia, in an attempt to prevent hypotension, is a common cause of fluid overload in otherwise healthy patients (Fig. 2), and may amount to several litres of fluid administered prior to surgery.[105] Several randomized clinical trials of preload *vs* no preload in women undergoing Caesarean section,[49 113] and elderly patients with hip fractures,[13] have found that a preload produces a marginal, if any, reduction in the incidence of hypotension. The lack of effect may be attributed to several factors, such as only a transient volume expansion from the infused fluids, or increased secretion of ANP.[105] Whatever the type of infused solution, rapid i.v. administration causes a significant increase in central venous pressure,[55] pulmonary wedge pressure[78] and haemodilution,[136] with possible detrimental consequences from increased lung water content.[75] A more rational approach may therefore be the use of vasopressors instead of a high-volume preload during regional anaesthesia. A randomized study comparing an ephedrine infusion with a 15 ml kg^{-1} crystalloid infusion in 54 patients undergoing elective gynaecological surgery with spinal anaesthesia, reported a significantly lower incidence of hypotension with the ephedrine infusion (22 *vs* 55%).[34]

Immobilization

Prolonged bed rest, which commonly occurs after major surgery, leads to a decrease in plasma volume of 300–500 ml, as well as a decrease in blood volume with negative sodium balance and loss of total body water.[18 82 83] These changes occur within the first few days of bed rest. Concomitantly, the extracellular volume has been found to be relatively increased compared with the intravascular volume during 1–2 weeks of bed rest.[37 81] The effect of bed rest on the hormones influencing fluid balance is debatable since either a small increase,[81] or no change,[18] in aldosterone and renin activity has been observed. Bed rest *per se* has been demonstrated to lead to a decrease in muscle potassium and intracellular water (intracellular dehydration) after 4 days of immobilization in healthy volunteers.[9] Exercise may improve renal osmolar clearance in healthy volunteers.[32] In another study in healthy volunteers, physical exercise after 7 days of bed rest had only negligible effects on fluid and ion balance compared with no exercise.[150] Further data from healthy volunteers indicate that mild exercise may increase urine flow and GFR above levels found at rest, and that only more severe exercise inhibits renal function, probably due to increased secretion of aldosterone and ADH, and a reduced GFR.[53]

The effects of immobilization on fluid balance *per se* have not been investigated in surgical patients, and whether fluid excretion is promoted by postoperative mobilization remains to be clarified. These issues may have important clinical implications due to the adverse effects on organ function of an inappropriate fluid overload. In contrast, an adequate intravascular volume is a prerequisite for mobilization. However, it may be hypothesized that a perioperative fluid excess may hinder postoperative mobilization due to the resulting increased cardiopulmonary demands of exercise.

Conclusions

So far, no widely accepted recommendations are available for the optimal perioperative fluid regimen. A large variability in fluid regimen has been noted throughout the surgical specialties. Except for the relatively 'dry' regimen that have been advocated in pulmonary surgery,[52 84 149] it has been common practice to administer relatively large amounts of fluid (regardless of blood loss or anaesthetic technique).[19 22 35 36 66 134] Preoperative dehydration from preoperative fasting (often for >12 h), bowel preparation or underlying illness certainly needs to be corrected.

On the other hand, perioperative administration of *large* amounts of crystalloids seems to have significant side-effects in several organ systems including the heart, primarily due to the potential impairment of left ventricular stroke volume, and the possibility of developing myocardial ischaemia. Pulmonary function may be impaired by accumulation of interstitial fluid, which may contribute to the development of pulmonary oedema, atelectasis, pneumonia or respiratory failure.[19] The resulting decreased tissue oxygenation may lead to impaired wound healing. Paralytic ileus may be prolonged by excess perioperative fluid administration.[70] Finally, excess fluid administration accentuates the water- and sodium-conserving effects of the surgical stress response, and may increase the risk of electrolyte disturbances such as hyponatraemia and metabolic acidosis.[20 118]

In contrast, the widespread use of 'dry' fluid regimen in pulmonary surgery with resulting decrease in pulmonary morbidity supports the safety of low-volume fluid regimen in high-risk patients undergoing major surgical procedures.

Achievement of optimal fluid status is not just a matter of fluid substitution *per se* but is also related to the

pathophysiology of the surgery. To clarify the implications of perioperative fluid excess, randomized, prospective clinical studies are needed where 'high' *vs* 'low' fluid regimen are undertaken in well-defined surgical procedures. Outcome assessments from studies of various organ dysfunctions and the associated morbidity are necessary to provide rational recommendations for perioperative fluid administration.

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