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VOLUME 1

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Foreword

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It is difficult to overestimate the importance of Continuing Medical Education and Professional Development (CEPD) for practising clinicians, and the major advances which continue to be made in anaesthesia and critical care must occupy a key role in this. It is all too easy for us, with the ever-increasing workload and demands of complex patient care, to feel we have no time to update our knowledge and skills, preferring to employ techniques with which we are familiar, supported by the sound clinical knowledge and judgment which we have acquired over many years. However, the development of anaesthetic techniques, equipment and pharmacology does not stand still. Equally, the sophistication of diagnostic techniques for our patients means that we are much better informed than in the past. In some ways, the more we know, the more difficult it is to make a balanced judgment on the optimal care of a patient. Yet how much more informative it is to know the actual gradient across a stenosed aortic valve than simply a judgment made on clinical signs. The demands made of anaesthetists both in theatre, in pain management and in the intensive care unit mean that being able to find sufficient time to attend CEPD meetings, particularly outside one’s own local environment let alone overseas, is increasingly difficult and therefore, for many of us, there is limited opportunity to concentrate and learn in an undisturbed way. Importantly, we need to hear the views of experts in their chosen field and, inevitably, we rely to a great extent on information supplied in academic journals and textbooks together, increasingly, from the Internet.

Unless one has an enormous amount of time and a range of journals available, it is often difficult to obtain a balanced view about new areas of anaesthesia and critical care. What we really need is an expert to assess the current topic in question and to produce an objective commentary and judgment on the various papers that have been written during recent months. The Year in Anaesthesia and Critical Care is, for me, a new concept of book-based CEPD, which concentrates on extracting information from a number of recent papers and assessing it in a meaningful and readable way. New books appear on a regular basis but most are either orientated towards examinations and assessment processes during training, or are expert textbooks in a particular field of either anaesthesia or critical care. Few are aimed at CEPD for established career grade clinical anaesthetists, but this, with its new innovative format and concept, is such a book.

No book of this nature should attempt to be comprehensive, and what the contributors have done is to select four key areas of recent development, namely perioperative care, anaesthetic pharmacology, new technologies in anaesthesia, and
critical care. Individual key subjects are dealt with in more detail within these four sections, and organised in each case by an editor who provides an excellent and objective editorial section at the beginning, including a brief overview of the subject, a summary of the papers, individual comment and references. The subject areas are reviewed by experts in the field who concentrate on a number of key publications that have occurred during the past year, looking at the key findings and recommendations of each and then coordinating these to provide more detailed response and comment. The reader is thus able to have expert opinion and comment at two levels both for the individual detailed subject area and more generally in the field which is the subject of the section of the book. Laid out as it is, in sections and subsections each with comprehensive headings, it is both easy to read and concentrate upon. Importantly, one only needs to read a small section at a time to gain relevant information, and interruptions do not disturb one’s flow of thought and learning unduly.

There is no doubt that the opportunity to concentrate on specific topical areas rather than the need to be comprehensive in terms of subject content makes for a much more readable and interesting publication. Even at the level of studying for examinations, key comment and essays from experts do much to help one’s understanding of a subject and the research and scientific basis behind new developments and techniques. This selective approach is exemplified in all parts of the book. The section on perioperative care, for example, concentrates on perioperative blood and intravenous fluid therapy and protecting the heart in coincidental surgical operations, together with one review specifically related to cardiac surgery. For clinical anaesthetists wishing to read material to increase their knowledge, this combination has all the right ingredients. It develops themes about which they already know a considerable amount but wish to be updated, leading them through new ideas and techniques. Finally, it provides a detailed look at a more specialist area of work which would be of interest even if they were not acutely involved with it. The second section on anaesthetic pharmacology follows a similar theme identifying clinical aspects of basic pharmacology, leading into discussions on some of the newer hypnotics and analgesics which will undoubtedly alter clinical practice in the future. Finally, it provides an update on the influence of pharmacogenetics on anaesthesia, a topic which is becoming increasingly important for us.

The section on new technology in anaesthesia and critical care is designed to take clinicians away from their current techniques, to show them what new developments have occurred and why these might be beneficial both for the quality of patient care and importantly for patient safety. This section then leads on to new equipment which few of us have had the opportunity of using. Although many of us are probably content to use our tried and tested techniques for central venous access and regional anaesthesia, if one talks to trainees, the vast majority find the use of ultrasound and Seldinger techniques second nature, and cannot imagine why we do not routinely use them in the same way. A book like this has the opportunity to discuss the advantages and disadvantages of new developments at length, and to try and reason through recent research and publications which inform the choice of technique. At present, there is considerable emphasis on the need to monitor depth of anaesthesia. Yet
informed judgment is undoubtedly necessary if we are to avoid simply purchasing vast numbers of monitors in response to external demands and pressures. It is for this reason as much as anything else that, as anaesthetists, we need to develop our thoughts and reasoning logically. We are very fortunate to have this undertaken for us in such a readable and understandable way. Although the last section contains a very valuable editorial on the issues surrounding critical care outreach and allows us to take a balanced view on its value in different hospitals, other articles in this section deal with a variety of other problems in intensive care medicine. Critical care outreach is again something about which one needs to make an informed judgment, before being pressurised to institute it, particularly if one feels that the decision to set up such a scheme is based upon little hard evidence and rather more on a perceived need because of a shortfall in ward-based care.

Review articles are an excellent way of keeping up to date and enhancing one's knowledge. Inevitably, they concentrate on specific topics and contain much of the authors' own opinions rather than looking at the variety of views from others and allowing the reader to exercise their own judgment. This book allows objective discussion and comment to be made about all the articles written around a certain subject by others. It then allows the reader to make a balanced judgment based upon the recommendations made. For continuous education to have an impact on one's opinion and clinical practice, one must be allowed to judge for oneself and not simply feel spoon-fed by others' opinions. The innovative format of this book, and the ease with which one can read and concentrate on it, makes it an ideal opportunity to enhance one's education in anaesthesia and critical care. The breadth of subjects covered will, I am sure, have widespread appeal.
Part I

Perioperative care
Perioperative care
HANS-JOACHIM PRIEBE

Introduction
Numerous aspects of management comprise perioperative care. This brief overview will concentrate on four broad topic areas: perioperative intravenous fluid therapy, perioperative blood transfusion therapy, off-pump coronary artery bypass surgery and perioperative cardiac protection.

Perioperative intravenous fluid therapy

Type of fluid
Even after decades of ongoing controversy, the debate on crystalloids versus colloids is still not settled. The debate is enlarged by the debate over the optimal type of crystalloid. Crystalloid administration may be associated with considerable adverse effects and these effects may differ considerably between different crystalloids.

Metabolic effects
Resuscitation with large volumes of high-concentration chloride solutions causes hyperchloraemic, non-anion gap metabolic acidosis. This type of acidosis may adversely affect urination, renal and gastric perfusion and function, pulmonary artery pressure and post-operative wellbeing. Lack of awareness of this condition may result in the erroneous diagnosis and treatment of presumed anion gap or respiratory acidosis.

Immunological effects
Different intravenous fluids have variable effects on immune function. This may be of considerable clinical relevance because trauma and surgery activate the immune system, which, in turn, may aggravate post-traumatic cell injury and organ dysfunction. It must be of concern that isotonic crystalloids (in particular lactated Ringer’s solution) can cause immune activation and cellular injury. The effect of hypertonic saline is less pronounced and plasma and albumin seem to be void of immune-activating activity. Lactated Ringer’s and hydroxyethyl starch solutions may even cause acute lung apoptosis.
The clinical relevance of these findings needs to be determined. Crystalloid solutions are being developed that not only possess volume-expanding but also anti-inflammatory characteristics.

**Haematological effects**

In general, non-protein colloids are associated with impaired haemostasis, platelet dysfunction and increased bleeding, while albumin and gelatins have the least effect. The effect of hydroxyethyl starch on coagulation is clearly dependent on the type of preparation, as defined by concentration (low 3%, medium 6% and high 10%), the degree of substitution of hydroxyethyl starch residues per mole of glucose (low 0.4, medium 0.5 and high 0.62–0.7), mean molecular weight (low 70 kDa, medium 130–260 kDa and high $\geq$450 kDa) and the ratio of C2:C6 hydroxyethylation.

**Conclusion**

It is highly unlikely that there will ever be an intravenous fluid that ‘fits all’. Only knowledge of the kinetics of fluid therapy, of the physico-chemical and pharmaco-kinetic characteristics of the fluids and of the pathophysiology of the underlying disease entity requiring fluid resuscitation will enable an appropriate choice and monitoring of volume replacement.

**Volume of fluid administration**

**The past**

It is still common practice to administer large volumes of fluid during elective surgical procedures. This practice is based on the paradigm upheld for many decades that surgical patients require high intra-operative fluid volumes, irrespective of specific haemodynamic measurements. This paradigm seemed to be supported by the principle of ‘goal-directed’ therapy, which improved outcome in high-risk surgical patients and in patients with severe sepsis and septic shock by ‘optimizing’ cardiac output.

However, data from studies involving patients with sepsis, shock and trauma cannot automatically be extrapolated to patients undergoing elective surgical procedures (and vice versa). Furthermore, most studies of goal-directed therapy have examined the effect of fluid therapy strategy in combination with inotropic support and the results of these studies have not been unanimous. Studies on goal-directed therapy looking at the influence of fluid administration alone have shown differences in the amount of perioperatively administered fluid between groups that were of questionable clinical relevance, which makes interpretation of the findings difficult. The most extensive recent trial on goal-directed therapy in major surgery not only failed to demonstrate benefit of such an approach, but pointed out some serious disadvantages.

The strategy of replacing blood loss by crystalloids at a 3:1 ratio is still common practice. Interestingly, the Saline versus Albumin Fluid Evaluation (SAFE) Study reported a mere 1.4:1 ratio of administered crystalloid:colloid. This finding is consistent with the possibility that the accepted practice of replacing blood loss with
crystalloids at a 3:1 ratio leads to clinically relevant acute over-transfusion with crystalloids.

**The present**

In contrast to what is commonly practised, there is now mounting evidence that the extracellular fluid shift ('third spacing') is less than previously assumed, that excess fluid can be detrimental and that excess perioperative fluid administration may worsen and fluid restriction may improve the perioperative outcome [17,18]. Thus, evidence suggests that careful perioperative fluid restriction may be indicated in selected patient populations undergoing selected elective surgical procedures. A decrease in perioperative urine output may often be a reflection of the perioperative stress response rather than of inadequate fluid therapy.

**Timing of volume administration**

The timing of volume of fluid resuscitation has recently received increasing attention. Inadequate fluid resuscitation (identified as being the most common management deficiency in trauma deaths) must be carefully weighed against increasing evidence that overly aggressive fluid replacement adversely affects the outcome in trauma patients [19,20].

**Perioperative blood transfusion therapy**

Although red blood cell transfusion increases oxygen-carrying capacity, a liberal transfusion strategy is usually not associated with improved outcome. This would suggest that either anaemia is beneficial or transfusion is detrimental. The beneficial effects of anaemia *per se* are difficult to postulate. On the other hand, the detrimental effects of transfusion leading to increased morbidity and mortality are well defined: infection, haemolytic reaction, contamination, allergic–anaphylactic reactions, transfusion-related lung injury [21] intravascular volume-related pulmonary oedema and immunomodulation.

**Transfusion trigger**

Uncertainty remains as to the appropriate haemoglobin (Hb) concentration that should trigger a blood transfusion. Despite evidence that a restrictive transfusion strategy (Hb 7.0–9.0 g/dl) lowers in-hospital mortality and reduces blood transfusions without adversely affecting the outcome in patients without cardiac disease [22], transfusion practice in the care of critically ill patients seems to have changed little during the past 10 years. Worldwide, the mean pre-transfusion Hb concentrations have consistently remained around 8.5 g/dl [23,24]. Only patients with acute coronary syndromes may benefit from a more liberal transfusion strategy [25–27].

**Immunomodulation**

Transfusion-related immune modulation is receiving continued and increasing attention. It is postulated that transfused allogeneic leucocytes trigger the immune
response, possibly resulting in more frequent infections, earlier development of malignancies and even increased mortality \(28,29\). Evidence does in fact suggest that universal leukoreduction may improve outcome \(30\) and, in particular, decrease post-transfusion non-haemolytic fever \(31-34\).

However, a recent meta-analysis of ten randomized trials did not demonstrate statistically significant benefits from leukoreduction \(35\). Leukoreduction was only associated with a 40% reduction in post-operative infections if the analysis was restricted to those patients who actually received blood transfusions. Although the scientific proof for the benefit of leukoreduction is still pending, based on existing evidence universal adoption of this practice has been recommended \(28\).

### Storage lesion

The clinical relevance of the blood ‘storage lesion’ possibly associated with the transfusion of ‘old’ blood continues to be debated. A blood storage lesion describes the reduced erythrocyte deformability caused by changes in the erythrocyte membrane due to storage-induced depletion of 2,3 diphosphoglycerol and adenosine triphosphate (ATP). Such erythrocyte defect may impair tissue oxygenation via impaired capillary blood flow and oxygen unloading from Hb.

The findings of two recent trials are controversial. One showed a trend towards a worse outcome in patients who received relatively old blood (mean age of blood 21 days) \(24\). The other did not show adverse effects of transfusion of stored, leukodepleted red cells to anaemic, critically ill patients on gastric tonometry and global indices of oxygen delivery \(36\). The issue remains far from being settled \(37\).

### Off-pump coronary artery bypass surgery

#### Who benefits?

Considerable progress has been made during the past years in the technique of coronary artery bypass graft (CABG) surgery without cardiopulmonary bypass (off-pump CABG or off-pump coronary artery bypass [OPCAB] surgery). The advance in the technique of OPCAB surgery is driven by the considerable risk of post-operative cognitive dysfunction and stroke associated with on-pump CABG in high-risk patients on the one hand and concern with poor long-term graft patency possibly associated with OPCAB on the other. Thus, a reduced incidence of post-operative cognitive dysfunction and stroke, combined with a comparable quality of revascularization surgery will be the ultimate criteria by which to judge the benefit of OBCAB over on-pump surgery \(38\).

Despite considerable effort and progress in this area, it may be somewhat disappointing that several recent randomized clinical trials comparing OPCAB to on-pump CABG surgery failed to document clear advantages of one technique over the other \(39-42\). Although OPCAB caused less myocardial damage than on-pump CABG and was as safe, the graft patency rates were lower at 3 months post-operatively,
which may adversely influence the long-term outcome [39]. There were no advantages of OPCAB over on-pump CABG in terms of morbidity (transfusion requirements, perioperative myocardial infarction, stroke, new atrial fibrillation and sternal wound infection), length of hospitalization and mortality [40,41].

A very recently published meta-analysis of 37 randomized trials involving 3369 patients confirmed the lack of difference between on-pump and off-pump CABG surgery in primary outcomes (mortality, myocardial infarction, stroke, renal dysfunction, requirement for an intra-aortic balloon pump, wound infection, rethoracotomy and reintervention) at 30 days and mortality at 2 years post-operatively [43]. Data on graft patency and post-operative cognitive function were inconclusive. Only selected short-term and mid-term clinical (atrial fibrillation, requirement for transfusion and inotropic support, respiratory infections, ventilatory support and length of stay in the intensive care unit and hospital) and resource outcomes favoured OPCAB surgery.

In contrast, most non-randomized trials (including large database observational studies) found significant differences in mortality, neurological, pulmonary, renal and bleeding complications usually in favour of the off-pump approach [44–47]. Particularly in subsets of patients considered to be at high risk for perfusion, off-pump surgery showed clear benefits [48,49]. Whereas in most randomized studies high-risk patients were excluded and the procedure-related risk was low for both procedures [43], the non-randomized trials contained relatively more high-risk patients in the on-pump groups than either the on- or off-pump groups in the randomized trials. Obviously, excluding high-risk patients from the randomized studies will make it more difficult for off-pump surgery to demonstrate superiority. Furthermore, in the randomized trials the mean age was only 63 years, the aggregate risk of stroke was only 1% (which is much lower than the usually reported rate of 2–3%), graft patency was not analysed quantitatively and the follow-up time was limited to 2 years.

Thus, the final verdict is not out yet. However, it is likely that different surgical approaches are indicated in different patient populations in order to optimize the short- and long-term outcomes [50]. Current evidence would suggest that, in good-risk patients, it is not worth compromising optimal revascularization for the purpose of performing surgery without cardiopulmonary bypass [51]. In contrast, patients with a risk of aortic cannulation or previous stroke and elderly patients may frequently benefit from the off-pump approach.

**Intra-operative management**

The success of OPCAB surgery will largely depend on optimal positioning of the heart in order to expose the target coronary vessel, on maximal reduction in local cardiac wall motion to perform the distal anastomosis and on techniques directed at minimizing myocardial injury during temporal occlusion of the target coronary artery necessary for visualizing the site of the distal anastomosis.

Lifting and rotating the heart and use of cardiac wall stabilization devices during OPCAB may impair cardiovascular performance, frequently requiring intravenous
administration of fluid and inotropic support and the Trendelenburg position. Displacement of the heart, fixation of the cardiac wall and temporary occlusion of the target coronary vessel contribute to impaired coronary blood flow and subsequent regional myocardial ischaemia, which, in turn, worsens haemodynamic instability [52].

With this much interference of routine surgery with cardiovascular performance, it is to be expected that, like the surgical, the anaesthetic management for OPCAB surgery is more demanding than that for on-pump CABG. Anticipation and intimate knowledge of the aetiology of the side effects associated with OPCAB-typical surgical interventions, close cooperation with the surgeon, preventive rather than therapeutic measures for counteracting the surgery-induced impairment in cardiovascular performance and, foremost, a highly skilled surgeon, are likely to affect outcomes more than a particular anaesthetic technique or drug.

**Perioperative cardiac protection**

The perioperative period induces large, unpredictable and unphysiological alterations in coronary plaque morphology, function and progression and may trigger a mismatch of myocardial oxygen supply and demand [53]. With many and diverse factors involved, it is highly unlikely that one single intervention will successfully improve cardiac outcomes following non-cardiac surgery. A multifactorial, stepwise approach is indicated.

Two principal strategies have been employed in an attempt to reduce the incidence of perioperative ischaemic cardiac events and complications: pre-operative coronary revascularization, and pharmacological treatment.

**Pre-operative coronary revascularization**

Controversy remains as to the appropriate management of patients identified pre-operatively as having relevant but correctable coronary artery disease (CAD). The effectiveness of pre-operative coronary revascularization in this population continues to be debated. Proponents of ‘prophylactic’ coronary revascularization in selected patients argue that it improves both perioperative as well as long-term outcomes [54]. Opponents of this approach point out that the morbidity and mortality of percutaneous coronary intervention and CABG surgery in high-risk elderly vascular patients are substantial and outweigh any benefit, that recovery from such major morbidity substantially delays and even prevents the surgery for which the intervention was undertaken, that it does not differentiate between young and old age and between patients with symptomatic CAD and those with CAD discovered by cardiac stress testing only, that only survivors of coronary revascularization are included in the various reports and, most importantly, that no prospective randomized trial exists that demonstrates the effectiveness of pre-operative coronary revascularization in improving the short- and long-term cardiac outcomes and mortality in high-risk patients undergoing high-risk surgery.
Pre-operative percutaneous intervention

Patients who have recently been subjected to coronary stenting run a high risk of suffering a perioperative myocardial infarction and serious bleeding (summarized in [53]). If a (bare metal) coronary stent is placed, elective non-cardiac surgery should, therefore, be delayed for an absolute minimum of 2 weeks, but ideally for 4–6 weeks. Today, stents eluting anti-proliferative drugs that delay endothelialization are increasingly being placed. As this may well increase the risk of early and late stent thrombosis, a 6–12-month period of anti-platelet treatment has been recommended [55,56].

Pre-operative surgical coronary revascularization

Survivors of coronary revascularization tend to have better perioperative and long-term cardiac outcomes than patients with comparable CAD without pre-operative coronary revascularization. However, this analysis does not take into account the high cardiac morbidity and mortality associated with pre-operative coronary angiography and coronary revascularization (pre-operative percutaneous intervention or CABG) in high-risk patients. In addition, survivors of pre-operative percutaneous intervention face the perioperative risk of coronary (stent) thrombosis or haemorrhage associated with discontinuation or continuation of dual anti-platelet therapy, respectively. The overall outcome may thus be comparable between pre-operatively revascularized and non-revascularized patients—it may be even worse in individual revascularized patients.

The first prospective, randomized trial demonstrated that prophylactic coronary revascularization before elective surgery does not alter the long-term outcome [57]. However, the patients were not selected according to the guidelines for pre-operative cardiac assessment issued by the American College of Cardiology and the American Heart Association [58] and less than half had significant CAD. Therefore, the applicability of the findings to high-risk patients remains unanswered.

The decision for or against pre-operative coronary revascularization and for or against pre-operative percutaneous intervention or CABG should therefore be based entirely on universally accepted medical indications for coronary revascularization and the appropriate technique. The philosophy of performing pre-operative coronary revascularization merely ‘to get the patient through surgery’ is contrary to all available evidence. If the decision for pre-operative coronary revascularization is made, timing with respect to the subsequent surgery appears crucial. If these caveats are being observed, it is conceivable that carefully selected patients might benefit from pre-operative coronary revascularization [54].

Pharmacological protection

Perioperative β-blocker therapy

Numerous cardiovascular and other effects (anti-arrhythmic, anti-inflammatory, altered gene expression and receptor activity and protection against apoptosis) of β-blockers may account for their cardioprotective effect in the operative and non-
operative setting [59]. Although perioperative β-blocker therapy has been designated as one of eleven specific practices with sufficient clinical-based evidence for patient safety to justify immediate and widespread implementation [60] and although its use continues to be highly recommended [61], the implementation of aggressive perioperative β-blocker therapy is slow [61–63].

However, before a final recommendation for liberal use of perioperative β-blockade can be made safely, several caveats have to be kept in mind (summarized in [53]). All studies that support the use of perioperative β-blocker therapy have included rather small numbers of patients (as few as 26). Often the recruitment of patients was highly selective and consecutive (recruitment rate as low as 8%), excluding application of the results to an unselected surgical population. Furthermore, the beneficial effects were probably not only due to a rather aggressive therapy (targeted heart rates maximally 80 beats/min), but also (and perhaps even more importantly) due to continuous close monitoring of the patient. This will ensure both optimal cardio-protection and patient safety. A more uncontrolled but equally aggressive postoperative administration of β-blockers on ordinary surgical floors might well result in more adverse side effects, possibly negating any beneficial effects. Although current evidence suggests that selected patients are likely to benefit from perioperative β-blocker therapy, we have to acknowledge that the data on the risks and benefits of such therapy are still few and inconclusive [64–66].

**α₂-adrenoceptor agonists**

α₂-adrenoceptor agonists may improve cardiovascular morbidity and mortality following non-cardiac and cardiac surgery [67]. The mechanism of the protective effect is likely to be manifold. α₂-adrenoceptor agonists attenuate perioperative haemodynamic instability, inhibit central sympathetic discharge, reduce peripheral norepinephrine release and dilate post-stenotic coronary vessels.

**Statins**

Perioperative use of statins may be associated with reduced perioperative mortality in patients undergoing major vascular and non-cardiac surgery [68–70]. ‘Pleiotropic’ effects of statins independent of their lipid-lowering action have been proposed as the mechanisms of their beneficial effects. These pleiotropic effects include reversal of endothelial dysfunction [71], modulation of macrophage activation [73], immunological effects [72] and anti-inflammatory properties [72,73], anti-thrombotic [71] and antiproliferative action (possibly mediated by the induction of haeme oxygenase-1) [74]. The direct effect of statins on vascular function may result in coronary plaque stabilization.

**Anaesthetic preconditioning**

An increasing number of experimental investigations demonstrate that volatile anaesthetics can acutely induce a cardioprotective memory effect that lasts beyond their elimination [75]. This mechanism attenuates the deleterious effects of myocardial ischaemia and reperfusion injury and is of considerable potential clinical
relevance. However, advanced age [76], diabetes mellitus [77], the use of oral hypoglycaemic drugs, the cardiodepressant effect of higher concentrations of volatile anaesthetics and the constraints of a complicated preconditioning protocol limits the applicability of this mechanism in routine clinical practice (for a review see [75]). We will have to await the results of large, well-designed clinical trials to see whether the results of basic research can be transferred into clinical practice.

**Conclusion**

The aetiology of perioperative ischaemic cardiac events is multifactorial [53,78]. The perioperative period induces large, unpredictable and unphysiological changes in sympathetic tone, cardiovascular performance, coagulation and inflammatory response (to name just a few). These changes in turn induce unpredictable alterations in plaque morphology, function and progression. Simultaneous perioperative alterations in homeostasis and coronary plaque characteristics may trigger a mismatch of myocardial oxygen supply and demand by numerous mechanisms. If not alleviated in time, it will ultimately result in myocardial infarction, irrespective of its aetiology (morphologically, haemodynamically, inflammatory or coagulation induced). With these many and diverse factors involved, it is highly unlikely that one single intervention will successfully improve cardiac outcome following non-cardiac surgery. A multifactorial, stepwise approach is indicated [79–81].

Based on increasing knowledge of the nature of atherosclerotic CAD and in view of the poor positive predictive value of non-invasive cardiac stress tests and the considerable risk of coronary angiography and coronary revascularization in high-risk patients, the paradigm is shifting from an emphasis on extensive non-invasive pre-operative risk stratification to an emphasis on a combination of selective non-invasive testing (to identify reliably those patients who truly benefit from pre-operative intervention, such as cancellation of surgery, pre-operative coronary revascularization and initiation or optimization of cardioprotective medication) and aggressive pharmacological perioperative therapy [81,82]). Perioperative plaque stabilization by pharmacological means (statins, aspirin and β-blockers) may be as important in the prevention of perioperative myocardial infarction as is an increase in myocardial oxygen supply (by coronary revascularization) or a reduction in myocardial oxygen demand (by β-blockers or α2-agonists).
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I. PERIOPERATIVE CARE


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Introduction

Perioperative volume deficits are common. Hypovolaemia may lead to maldistribution of the blood flow, which prevents the circulation fulfilling its nutritive role. Many manifestations of organ failure after seemingly successful primary resuscitation may result from peripheral (micro-) circulatory derangements (Fig. 1.1). Restoration of ‘normal’ systemic haemodynamics is not necessarily accompanied by restoration of organ and tissue perfusion. During low output states the organism compensates for perfusion deficits by redistribution of the blood flow to vital organs (e.g. the heart and brain) at the expense of under-perfusion of non-vital organs (the splanchnic bed and kidney).

Inflammatory mediators and vasoactive substances are released in this situation and contribute to the development of impaired perfusion. Activation of the sympathetic nervous system and the renin–angiotensin system are compensatory mechanisms for maintaining peripheral perfusion. Although such compensatory neurohumoral activation is beneficial at first, it may however contribute to an adverse outcome in the hypovolaemic surgical patient, even after initially successful volume resuscitation.

Controversy continues about what constitutes the ideal volume replacement regimen. Crystalloids (e.g. normal saline and Ringer’s lactate), the natural colloid human albumin, synthetic colloids (dextran, gelatins and hydroxyethyl starch preparations) (Fig. 1.2) and hypertonic solutions are all available for treating perioperative volume deficits. All plasma substitutes have their merits and demerits. Some well-known side effects (e.g. bleeding following the administration of dextran) considerably limit the routine use of some of them.

A new controversy surrounds the adequate amount of perioperative fluid administration. For decades the philosophy has been to keep the patient normovolaemic (‘well hydrated’) in the perioperative period. Newer findings now suggest that keeping the patient ‘dry’ may improve outcomes.

Overall evidence indicates that an adequate volume replacement therapy is a cornerstone in the management of the surgical patient. It is a prerequisite in the
efforts at improving organ function and reducing patient morbidity and possibly even mortality. However, in a prospective review of 111 consecutive in-hospital deaths in trauma patients, inadequate fluid resuscitation was the most common management failure [1].

**What is the ideal substance for perioperative fluid therapy?**

**Haemodynamic efficacy**

Due to their different physico-chemical characteristics the various solutions differ in their haemodynamic efficacy. After infusion, crystalloids rapidly shift from the
intravascular to the interstitial compartment and subsequently possess only a limited volume-replacing capability. Consequently, if hemodynamic stability is to be guaranteed, crystalloids have to be administered at three to five times the volume lost. Due to the subsequent interstitial dilution the interstitial colloid oncotic pressure decreases, resulting in interstitial edema formation. According to their widely differing colloid oncotic pressures, colloids are separated into hypo-oncotic (e.g. 3.5% gelatine and 4% albumin), iso-oncotic (e.g. all 6% hydroxyethyl starch preparations) and hyperoncotic (e.g. 10% hydroxyethyl starch preparation, 10% dextran and 20% human albumin). Colloids also differ in their water-binding capacity.

**Fig. 1.2** The physico-chemical characteristics of hydroxyethyl starch solutions have changed over the years resulting in different generations of hydroxyethyl starch solutions with different concentrations (3, 6 and 10%), mean molecular weights (70, 200 or 130 kDa) and molar substitutions (e.g. 0.5, 0.62 or 0.7).

3.5% urea-linked gelatin is as effective as 6% HES 200/0.5 for volume management in cardiac surgery patients


**Background.** The efficacy of volume expansion with either 3.5% gelatine (25.8 ± 4.8 ml/kg) or 6% hydroxyethyl starch 200/0.5 (24.5 ± 6.0 ml/kg) was assessed in patients undergoing cardiac surgery. The second objective was to compare blood loss and the allogeneic blood transfusion exposure rate.

**Interpretation.** Hydroxyethyl starch was not associated with a better plasma expansion than gelatine, but resulted in a higher need for allogeneic blood transfusion.
The finding of comparable haemodynamic effects is surprising because several previous studies have shown a lower volume-replacing efficacy of gelatine than of hydroxyethyl starch (Fig. 1.3). The molecular weights of gelatins range from 5000 to 50,000 Da, with a weight-average molecular weight of 30,000 to 35,000 Da. As the molecular weight is lower than the renal threshold, gelatins are rapidly cleared from the bloodstream by glomerular filtration, resulting in the shortest intravascular half-life (less than 2 h) of all colloids.

The finding of a significantly higher total blood loss in the hydroxyethyl starch group (11.0 ± 7.8 ml/kg) than in the gelatine group (8.7 ± 4.0 ml/kg) is equally surprising. A previous meta-analysis showed that blood loss in cardiac surgery is comparable during volume therapy with either 6% hydroxyethyl starch 200/0.5 or human albumin, the ‘gold standard’ of volume therapy that did not negatively affect coagulation.

**Comment**

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**Side effects of plasma substitutes used for treating perioperative hypovolaemia**

**Bleeding**

For numerous reasons the surgical patient is at increased risk of developing coagulation abnormalities perioperatively, resulting in an increased bleeding tendency. All fluids used for volume replacement lower the plasma concentration of clotting proteins by haemodilution. Some fluids possess additional specific (negative) effects on
haemostasis (e.g. dextrans). Albumin and gelatins appear to be almost void of relevant negative effects on haemostasis. The continued reluctance to use hydroxyethyl starch for volume replacement is based on reports of abnormal coagulation and the increased bleeding tendency associated with its use [4,5].

However, such findings were probably related to the use of first-generation, high molecular weight (mean molecular weight 450 kDa), high degree of molar substitution (>0.62) preparations. Recent studies using newer hydroxyethyl starch preparations have shed new light on this issue. A modified first-generation high molecular weight hydroxyethyl starch (Hextend™) (molar substitution 0.7, weight-average molecular weight approximately 670 kDa and mean molecular weight 550 kDa) impaired coagulation less than conventional first-generation high molecular weight hydroxyethyl starch (Hetastarch) [5]. Similarly, a third-generation, low molecular weight (molecular weight 130 kDa), low substitution (molar substitution 0.4) hydroxyethyl starch preparation [6] appeared to be associated with less adverse effects on coagulation and post-operative bleeding [7–12].

**Inhibition of platelet function by hydroxyethyl starch solutions in chronic pain patients undergoing peridural anesthesia**


**Background.** The effects of 6% hydroxyethyl starch (molecular weight 130 kDa and molar substitution 0.4), 6% hydroxyethyl starch (molecular weight 200 kDa and molar substitution 0.62) and lactated Ringer’s solution (10 ml/kg each administered intravenously for 30 min) on platelet function (using the platelet function analyser PFA-100®) and haemodynamics were studied in patients with chronic low back pain scheduled for peridural analgesia.

**Interpretation.** Low and medium molecular weight hydroxyethyl starch solutions inhibited platelet function. This effect was more pronounced during administration of hydroxyethyl starch 200/0.62 than administration of hydroxyethyl starch 130/0.4.

**Comment**

Although the changes in the platelet function analyser closure times (a marker for platelet function) after infusion of 6% hydroxyethyl starch 130/0.4 were significant, they were small and the mean data remained within the normal range. In contrast, the changes induced by hydroxyethyl starch 200/0.62 were more pronounced and sometimes exceeded normal values. Interestingly, previous studies from the same group of investigators [7] and from other investigators [8–12] have not reported adverse effects of the newest generation of hydroxyethyl starch (hydroxyethyl starch 130/0.4) on platelet function [7], haemostasis [7–12] and bleeding [7–12]. Unfortunately, the number of patients in this study by Scharbert et al. was too small to allow valid con-


The effects of high molecular weight hydroxyethyl starch solutions on platelets

**Background.** The anti-platelet effect of a novel high molecular weight, balanced hydroxyethyl starch preparation (Hextend™) was studied in vitro. For this purpose the availability of the glycoprotein IIb–IIIa receptor was assessed on non-stimulated and on agonist-induced platelets using flow cytometry.

**Interpretation.** Hextend™ showed an unexpected platelet-stimulating effect that is unique among the currently available hydroxyethyl starch preparations. This effect may be induced partly by its solvent containing calcium chloride dihydrate.

**Comment**

The adverse effects of hydroxyethyl starch on haemostasis appear to depend on its mean molecular weight and molar substitution. Higher values of these factors lead to greater expected adverse effects [13-15]. Most reports of impaired haemostasis are based on the study of first-generation high molecular weight, highly substituted hydroxyethyl starch (Hetastarch). Infusion of such a hydroxyethyl starch preparation may result in a type I Von Willebrand-like syndrome with reduced factor VIII coagulant activity and decreased Von Willebrand’s factor VIII-related antigen and factor VIII-related ristocitin cofactor [13,14]. In addition, large amounts of high molecular weight hydroxyethyl starch caused platelet swelling and reduced platelet adhesion [13,14]. In contrast, low molecular weight hydroxyethyl starch influences the concentrations of VIII-related antigen and VIII-related ristocitin cofactor significantly less than high molecular weight hydroxyethyl starch [13,14].

The hydroxyethyl starch in Hextend™ is a high molecular weight hydroxyethyl starch with a very high molar substitution (0.7). It is surprising that small amounts of a solvent would be able to blunt the negative effects of this hydroxyethyl starch preparation on haemostasis. Other investigators were unable to confirm that modification of a high molecular weight hydroxyethyl starch (Hextend™) eliminates the negative effects on coagulation [16]. Furthermore, the clinical relevance of such in vitro findings has to be questioned: in vivo endothelial cell and neurohumoral function markedly modify the coagulation process and, subsequently, interact with the effects of plasma substitutes on haemostasis.
**Differential platelet receptor expression following hydroxyethyl starch infusion in thrombocytopenic orthotopic liver transplantation recipients**


**BACKGROUND.** After orthotopic liver transplantation, patients present with thrombocytopenia and associated bleeding problems which may be aggravated by the interaction of hydroxyethyl starches with platelets. Surface expression of glycoprotein IIb/IIIa and P-selectin were quantified by flow cytometry and the percentage of platelet-leukocyte complexes.

**INTERPRETATION.** Infusion of 6% hydroxyethyl starch 200/0.5 in clinically relevant doses (10 ml/kg) did not alter glycoprotein IIb/IIIa expression in thrombocytopenic patients with pre-existing platelet dysfunction after orthotopic liver transplantation.

**Comment**

In contrast to the *in vitro* study discussed above [17], this *in vivo* study did not demonstrate any adverse effect of 6% hydroxyethyl starch 200/0.5 on platelet function. Infusion of this preparation may possibly exert a beneficial effect on microvascular graft perfusion, resulting from the haemodilution and reduced P-selectin expression. The latter may, in turn, reduce leukocyte-platelet complexes and endothelial adhesion.

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**Volume efficacy and reduced influence on measures of coagulation using hydroxyethyl starch 130/0.4 (6%) with an optimised *in vivo* molecular weight in orthopaedic surgery: a randomised, double-blind study**


**BACKGROUND.** The differences between different hydroxyethyl starch preparations on blood coagulation may partly be related to their different *in vivo* molecular weights.

**INTERPRETATION.** Hydroxyethyl starch 130/0.4 and hydroxyethyl starch 200/0.5 showed comparable volume efficacy. However, sensitive coagulation parameters returned more rapidly to normal in the hydroxyethyl starch 130/0.4-treated patients than in the hydroxyethyl starch 200/0.5-treated patients.

**Comment**

This double-blind study demonstrated that hydroxyethyl starch 130/0.4 is superior to the second-generation hydroxyethyl starch 200/0.5 with regard to certain coagul-
tion data: in contrast to the hydroxyethyl starch 200/0.5 group, in the hydroxyethyl starch 130/0.4 group factor VIII and Von Willebrand factor had returned to near baseline values by 5 h post-operatively. Lower in vivo molecular weight and more rapid excretion of hydroxyethyl starch 130/0.4 are the likely explanations for the smaller influence on coagulation. Consistent with these findings, there was a (statistically non-significant) trend towards lower blood loss in the hydroxyethyl starch 130/0.4 group. Other investigators have confirmed these beneficial effects [18,19].

**Hydroxyethyl starch as a priming solution for cardiopulmonary bypass impairs hemostasis after cardiac surgery**


**BACKGROUND.** Hydroxyethyl starch is often reported to impair coagulation and increase the bleeding tendency in cardiac surgery patients.

**INTERPRETATION.** A dose of 20 ml/kg of low molecular weight hydroxyethyl starch (molecular weight 120 kDa and molar substitution 0.7) and high molecular weight hydroxyethyl starch (molecular weight 400 kDa and molar substitution 0.7) added to the cardiopulmonary bypass prime compromised haemostasis after cardiac surgery more than equal amounts of 4% human albumin. This effect appeared to be related to the formation of a less stable thrombus.

**Comment**

Thrombelastogram was used for assessing the influence of the three plasma substitutes on coagulation. The reaction time ($r$) and coagulation time ($r + k$) did not differ between the groups. Only the maximal amplitude and speed of solid clot formation (alpha angle) were different between the hydroxyethyl starch- and albumin-treated patients. However, the normal range of thrombelastogram values was not provided and the differences were rather small (e.g. maximal amplitude values of 46 and 40 for albumin and hydroxyethyl starch 120/0.7, respectively). Bleeding did not differ significantly between the albumin- and hydroxyethyl starch 120/0.7-treated patients, but was higher in the hydroxyethyl starch 400/0.7 group, confirming data from a meta-analysis [4]. The results of this study suggest that high molecular weight, high substitution hydroxyethyl starch preparations should be avoided in cardiac surgery.

**Additional effects of plasma substitutes**

Besides its haemodynamic effects, those on organ perfusion and microcirculation may be as important when looking for the optimal volume replacement strategy [20].
However, microcirculation, organ perfusion and tissue oxygenation are difficult to assess in humans. Unspecific surrogates are mostly used (e.g. gastromucosal tonometry [pHi]). Whether such surrogates reflect tissue perfusion and correlate with outcomes remains to be determined.

In addition to improving organ perfusion and the microcirculation, optimization of the intravascular volume may have an important impact on immune responses. In this regard, the amount rather than the composition of the administered fluid is assumed to be the main determinant. However, only a few studies have focused on this aspect of volume replacement therapy.

### The effects of hydroxyethyl starch on lung capillary permeability in endotoxic rats and possible mechanisms


**BACKGROUND.** The effects of hydroxyethyl starch 200/0.5 on lung capillary permeability in endotoxic rats (induced by lipopolysaccharide) were studied.

**INTERPRETATION.** Hydroxyethyl starch 200/0.5 reduced increased lung capillary permeability in endotoxaemia, most likely due to an anti-inflammatory effect.

**Comment**

In this investigation in rats, hydroxyethyl starch 200/0.5 at doses of 3.75 and 7.5 ml/kg ameliorated lipopolysaccharide-induced increases in lung capillary permeability. Hydroxyethyl starch inhibited lung neutrophil accumulation, cytokine-induced neutrophil chemoattractant protein, NF-κB activation and CD11b expression in a dose-dependent manner. Lack of immunosuppression by synthetic colloidal fluids has previously been suggested by findings of unimpaired T-cell activation and mitogenic response during the administration of dextran, gelatins or hydroxyethyl starch 450/0.7 [22,23]. Furthermore, hydroxyethyl starch did not affect the time- and dose-dependent generation of a chemotactic cytokine and did not by itself induce cytokine generation or change human monocyte chemotaxis and spontaneous migration [24].

In patients undergoing minor urological surgery, different hydroxyethyl starch preparations (hydroxyethyl starch 70/0.5, 200/0.5 and 450/0.7) did not affect the phagocytic activity of polymorphonuclear neutrophils (PMNs). In contrast, gelatine decreased the phagocytic capacity of both neutrophils and monocytes [25]. Evidence would thus suggest that hydroxyethyl starch might be used in patients at increased risk of inflammatory response.
Influence of different volume replacement strategies on inflammation and endothelial activation in the elderly undergoing major abdominal surgery


BACKGROUND. Major surgery activates an inflammatory cascade, which in turn triggers counter-regulatory mechanisms that are aimed at controlling the intensity of the inflammatory response. Different intravenous fluids may have different effects on the inflammatory response.

INTERPRETATION. In elderly surgical patients, volume replacement with a third-generation hydroxyethyl starch preparation (6% hydroxyethyl starch 130/0.4) was associated with a lesser inflammatory response (lower concentrations of interleukins) and endothelial injury/activation (lower concentrations of circulating adhesion molecules) compared to volume replacement with either Ringer’s lactate or normal saline.

Comment

The reasons for the different inflammatory response and endothelial injury/activation between the hydroxyethyl starch- and crystalloid-treated patients remain unclear. The microvasculature is a key ‘battleground’ for the inflammatory response, with evidence of a central role for the endothelium in modulating inflammation. The hydroxyethyl starch molecule may exert a direct, substance-specific effect on endothelial cells resulting in a decreased release of adhesion molecules. The beneficial effect may also be due to improved organ function (e.g. via improved splanchnic perfusion) and microcirculation.

Intra-operative colloid administration reduces post-operative nausea and vomiting and improves post-operative outcomes compared with crystalloid administration


BACKGROUND. The choice of intravenous fluid may affect the post-operative patient recovery profile.

INTERPRETATION. In patients undergoing major elective non-cardiac surgery, administration of a non-balanced, standard hydroxyethyl starch solution (1301 ± 1079 ml) or a balanced hydroxyethyl starch solution (1448 ± 759 ml) was associated with a lower incidence of nausea and vomiting, use of rescue anti-emetics, severe pain, periorbital oedema and double vision compared to crystalloid administration (5946 ± 1909 ml Ringer’s lactate).
Comment

This is the first study to suggest that the choice of intravenous fluid may affect post-operative recovery and that colloids may, in this regard, be superior to crystalloids. However, additional studies are required before a final conclusion is possible.

Does albumin have a place for treating the hypovolaemic patient?

Albumin is still widely considered the ‘best’ solution, particularly in the critically ill with compromised organ function. However, cost containment is becoming increasingly important in medical decision making. Although comparison of costs is very difficult because of local differences in medico-economic systems, albumin is considerably more expensive than modern synthetic colloids.

Consequently, albumin use has declined over the past few years. Not surprisingly, the albumin industry launched an international promotion programme worth US$ 2.2 million in order to promote albumin, triggering the publication of several studies that addressed the value of albumin, several of them, however, being reviews, retrospective analyses or meta-analyses. The Cochrane Injuries Group published a meta-analysis (including 30 studies with a total of 1419 patients) that compared albumin with other intravenous volume replacement fluids (crystalloids and synthetic colloids). The use of albumin was associated with an overall excess mortality of 6.8% (or approximately six additional deaths for every 100 patients treated with albumin). It is beyond the scope of this review to address the topic of correction of hypoproteinaemia in the critically ill intensive care patient.

Safety of human albumin—serious adverse events reported worldwide in 1998–2000


Background. All serious adverse event reports and total doses of albumin distributed worldwide from the beginning of 1998 to the end of 2000 were reviewed.

Interpretation. Within a total distribution group of 1.62 × 10^7 units of albumin, 198 non-fatal and 13 fatal serious adverse events were reported, amounting to an incidence of 5.28 per 10^6 doses and 4.65 per 10^6 doses for serious non-fatal and fatal adverse events, respectively. No patient death was attributed directly to albumin administration.

Comment

This study was supported by a grant from the Plasma Protein Therapeutics Association. The findings are in complete contradiction to those of the meta-analysis by the Cochrane Injuries Group, which suggested that albumin might be increasing
mortality [29]. There was no differentiation between treatments for hypovolaemia or hypoproteinaemia.

Volume expansion with albumin decreases mortality after coronary artery bypass graft surgery


**Background.** As albumin and non-protein colloids (starches, dextran and others) are used frequently as blood volume expanders in coronary artery bypass graft (CABG) surgery, this study aimed at determining differences between colloids with regard to patient characteristics and mortality rates.

**Interpretation.** In this retrospective analysis of 19,578 patients undergoing CABG surgery, mortality was lower in the albumin (n = 8084) than in the non-protein colloid group (2.47 versus 3.03%) (P = 0.02), which included first-generation hydroxyethyl starch 450/0.7 and dextrans. Albumin was associated with 25% lower odds of mortality compared to non-protein colloid use (odds ratio 0.80 and 95% confidence interval [CI] 0.67–0.96).

**Comment**

This retrospective analysis had several limitations. No information regarding preoperative myocardial infarction, congestive heart failure and renal failure was provided. As the authors did not differentiate between the non-protein colloids (hydroxyethyl starch versus dextran), it is impossible to determine which group had the highest mortality. Both non-protein colloids used in this study are known to interfere with the coagulation cascade resulting in an increased bleeding tendency [30]. Accordingly, the blood transfusion requirements were three times lower in the albumin than in the non-protein colloid groups. Use of non-leukocyte-depleted packed red blood cells is associated with several adverse effects [31,32], including increased inflammation and impaired coagulation. Thus, the higher number of transfusions in the non-protein colloid groups might have been responsible for the differences in mortality. It is conceivable that, had albumin been compared with a modern colloid (e.g. hydroxyethyl starch 130/0.4), the results might have been different.

A comparison of albumin and saline for fluid resuscitation in the intensive care unit


**Background.** Volume therapy using 4% albumin was compared with normal saline solution in approximately 7000 critically ill intensive care unit (ICU) patients in a multicentre, randomized double-blind trial.
**Interpretation.** In a heterogeneous population of ICU patients (43% surgical and 57% medical patients), fluid resuscitation with either 4% albumin or normal saline resulted in comparable 28-day morbidity and mortality. Length of stay in the ICU and in the hospital as well as days on the ventilator and days on renal replacement therapy were also comparable.

**Comment**

Although this study in hypovolaemic ICU patients was not directly related to the topic of perioperative fluid replacement therapy, it deserves mentioning because it is the largest available study to date on volume replacement strategies. Although the results seriously question any advantage of albumin over crystalloids in the critically ill, the results are not necessarily applicable to all colloids. It is questionable whether 4% albumin is the ideal colloid for treating the hypovolaemic critically ill. Moreover, the criteria for volume replacement were not strictly defined (no ‘goal-directed’ volume therapy) and the ratio of administered albumin to crystalloids was 1:1.4. Considering usually accepted ratios of between 1:3 and 1:5, it is possible that the patients receiving crystalloids were insufficiently volume resuscitated. Thus, even the SAFE (Saline versus Albumin Fluid Evaluation) Study is unable to settle the ‘age-old’ crystalloid versus colloid debate.

**Hypertonic volume replacement strategy**

Enthusiasm has surrounded the treatment of hypovolaemic shock with hypertonic or hypertonic–hyperoncotic solutions. The sodium concentrations of these solutions range from 3 to 7.5%. Hypertonic solutions appear to improve cardiovascular function by multiple mechanisms.

1. The displacement of tissue fluid into the blood compartment with subsequent plasma volume expansion (main mechanism).
2. Direct vasodilatory effects in the systemic and pulmonary circulation.
3. A reduction in venous capacitance.
4. Positive inotropic effects through direct actions on myocardial cells.

Due to the hypertonicity of the solutions, only a small volume of fluid (approximately 4 ml/kg) is required for restoring cardiovascular function effectively (the principle of ‘small volume resuscitation’). The initial improvement in cardiovascular function (e.g. increase in cardiac output) seems to be mediated by the hypertonicity rather than by the solute composition of the solution. As the beneficial effects of hypertonic solutions seem to be rather transient, hypertonic solutions were mixed with colloids (dextran or hydroxyethyl starch), which significantly prolonged their action.
Hypertonic versus near isotonic crystalloid for fluid resuscitation in critically ill patients

Background. Due to their physico-chemical properties, rapid administration of small volumes of hypertonic solutions may be superior to the administration of crystalloids in expanding blood volume and elevating blood pressure.

Interpretation. This meta-analysis reviewed 14 randomized trials (including a total of 956 patients) that compared hypertonic with isotonic and near-isotonic crystalloids in patients with trauma, burns or undergoing surgery. The pooled relative risk for death was 0.84 in trauma patients (95% CI 0.69–1.04), 1.49 in burn patients (95% CI 0.56–3.95) and 0.51 in patients undergoing surgery (95% CI 0.09–2.73).

Comment
This review did not provide sufficient data for allowing final judgement as to whether a hypertonic crystalloid is better than isotonic and near-isotonic crystalloids for the resuscitation of patients with trauma, burns or those undergoing surgery. As mortality was not the primary outcome variable in most studies on volume replacement regimens, the validity of meta-analyses that focus on mortality has been questioned.

Is less more or is more better?
The ‘dry versus wet’ philosophy in managing the surgical patient has spiked enormous interest in recent years. Intravenous fluid overload in the perioperative period is associated with decreased tissue oxygen tension, delayed recovery from gastrointestinal function and even adverse outcomes. On the other hand, inadequate volume resuscitation of the critically ill patient undergoing major surgery may equally result in organ dysfunction and an adverse outcome.

The microcirculation represents the final common pathway of the respiratory and circulatory system. Under certain conditions (e.g. shock, ischaemia and cardiopulmonary bypass), interactions between the endothelium and cellular elements of the blood and endothelial swelling prevent effective microcirculatory flow. Poor capillary perfusion impairs oxidative killing in the wound and triggers additional release and activation of mediators that subsequently promote cell adhesion and vaso-
constriction. Increased permeability ('capillary leakage') causes endothelial swelling in the capillaries. The deteriorated microcirculation initiates a vicious cycle of progressive tissue damage that may ultimately lead to the development of multiple-organ failure.

**Effects of intravenous fluid restriction on post-operative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial**

**BACKGROUND.** As the amount of perioperatively administered fluid may affect outcomes, the effects of a restricted versus a standard intravenous fluid regimen were compared in patients undergoing colorectal resection.

**INTERPRETATION.** In this randomized observer-blinded multicentre trial in 141 patients restricted perioperative fluid administration (median 2740 ml and range 1100–8050 ml versus median 5388 ml and range 2700–11 083 ml in the control group) was associated with fewer post-operative complications. The mortality was comparable between the groups.

**Comment**
The total number of major complications (see Table 1.1) was significantly lower in the fluid-restricted than in the standard group.

The main limitation of the study was the administration of fixed amounts of fluid rather than 'goal-directed' fluid administration. Due to the fixed-volume replacement protocol, some patients were likely to have been fluid overloaded. The range of values of administered volume indicates significant overlap between groups. In fact, 15% of patients in the 'restricted group' received more volume, while 24% of the 'standard group' received less volume than dictated by the protocol. No haemo-

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<tr>
<th>Complication</th>
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<tr>
<td>Sepsis</td>
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<td>Bradycardia</td>
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Source: Brandstrup et al. (2003).
dynamic data (e.g. central venous pressure and cardiac output) were provided. Goal-directed volume therapy in the critically ill \cite{39} and pre-operative increases in cardiac output to ‘supra-normal’ values (particularly in critically ill patients undergoing complex surgical procedures) \cite{40,41} may improve outcome.

**Supplemental perioperative fluid administration increases tissue oxygen pressure**


**Background.** Hypoperfused tissues experience low oxygen tension that is insufficient for allowing adequate oxidative killing or wound healing. The hypothesis was tested that supplemental perioperative fluid administration increases tissue perfusion and tissue oxygen pressure.

**Interpretation.** ‘Aggressive’ fluid management (10 ml/kg of crystalloids given prior to surgery and 6–18 ml/kg/h given intra-operatively and during the first post-operative hour) in patients undergoing colon resection resulted in higher muscle tissue oxygenation (measured at the patient’s upper arm) than conservative fluid management (8–10 ml/kg/h of crystalloids). The findings indicate that supplemental perioperative fluid administration may significantly increase tissue perfusion and tissue oxygen partial pressure. Optimizing tissue perfusion will require providing more fluid than may be indicated by the usual clinical criteria or routine invasive monitoring.

**Comment**

Improved tissue perfusion and oxygenation can be expected to be of particular benefit in patients who are at increased risk of reduced tissue perfusion (e.g. patients with diabetes mellitus). Even moderate hypovolaemia (that is sometimes difficult to recognize clinically) may be associated with a seriously impaired microcirculation. It is important to note that no colloids were administered throughout the study. However, colloids may improve tissue oxygenation more than crystalloids \cite{42,43}. It remains to be determined whether muscle tissue oxygenation reflects tissue oxygenation in other, clinically more relevant organs.

**Conclusion**

The beneficial and adverse effects of the various types of fluid continue to be debated \cite{44}. Besides the natural colloid albumin, several synthetic colloids are increasingly being used as plasma substitutes. A colloid versus colloid debate can now be added to the age-old crystalloid versus colloid debate. Several messages can be extracted from the recent publications on perioperative volume replacement therapy.

1. Crystalloids may adversely affect coagulation (hypercoagulability) and the metabolic state (acidosis). They seem to lack beneficial effect on the microcirculation
and organ perfusion. Even ‘aggressive’ administration of large amounts of crystalloids may not adequately restore microcirculatory blood flow.

2. Hydroxyethyl starch is the most studied plasma substitute. Conflicting results regarding its effects on various organ perfusions and functions are mostly due to the use of different hydroxyethyl starch preparations and varying study designs.

3. Available evidence does not support the use of albumin over less expensive alternatives in treating perioperative hypovolaemia.

4. It remains to be determined whether the quantity or composition of the intravenous fluid is the main determinant of the treatment effectiveness in the hypovolaemic critically ill patient.

We are living in an era of meta-analyses and evidence-based medicine. At times this has produced more confusion than it has help in finding the optimal volume replacement regimen. Although the quality of study design has improved, standardized protocols for volume replacement are frequently still missing. The choice for or against a particular intravenous fluid should take into account its effects on tissue perfusion, organ perfusion and function, endothelial function, inflammatory response and various other physiological variables. The challenge will be to determine which patients benefit most from which type of volume replacement strategy.

References


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