Perioperative Fluid and Electrolyte Management in Cardiac Surgery: A Review

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Abstract: This article can be broken down into three sections. First is a review of extracellular fluid volume management and some of the key physiological principles involved. Second, there is an appraisal of the merits or otherwise of crystalloids and colloids for volume replacement, and finally, a summary of the key points in our appreciation of the behavior of various cations in the perioperative period. In all these areas, there has been much academic endeavor. Sometimes this has generated more heat than light, and the lack of consensus in many areas serves to highlight the need for further work and better understanding. Keywords: hetastarch, albumin, cardiopulmonary bypass, prime.

Perioperative fluid and electrolyte management is, on the face of it, a simple matter of replacing calculated losses and targeting recognized normal physiological values as an end point. In the real world, things are far more complex. The perioperative period is a highly dynamic time with the perturbations of anesthesia, cardiopulmonary bypass, and the surgery itself. Added to this are such variables as the patient’s preoperative condition and the effects of the postoperative surgical stress response. As clinicians, we are faced with much uncertainty. Published research is often limited, conflicting, and, occasionally, fraudulent. There remains some uncertainty as to our targeted end points, and our ability to measure them accurately has, until relatively recently, been limited. The replacement fluids we have at our disposal are far from perfect. The great fluid debate rages on.

FLUID REPLACEMENT

Physiological Considerations

The aim of fluid replacement is to maintain the extracellular volume. This can be broken down into the intravascular or plasma volume and the extravascular or interstitial fluid volume. Maintenance of plasma volume is important for the delivery of an adequate preload to the heart to optimize ventricular contractility and cardiac output. Adequate intravascular volume is also required for optimal tissue oxygen delivery. However, tissue oxygen delivery will be compromised by an excessive interstitial fluid volume because this will lead to edema, compression of the microvasculature, and increases in oxygen diffusion distances. Losses from the intravascular space can be measured as they occur. In contrast, changes in the interstitial volume can only be estimated.

The capillary endothelium acts as the barrier between intravascular and interstitial fluids. A model for the movement of fluids across the endothelium was described by Starling in 1896 (1). Water, electrolytes, and small-molecular-weight molecules pass freely between the two spaces under the influence of hydrostatic and oncotic pressure gradients, both of which are initially much greater on the intravascular side of the endothelium. Net flow of fluid out of the proximal capillary resulting from the hydrostatic pressure gradient leads to a fall in the intraluminal hydrostatic pressure and a rise in the oncotic pressure resulting from concentration of the osmotically active substances remaining within the lumen. This, in turn, leads to a reversal of flow in the distal capillary. The overall result is a small net flow of fluid into the interstitial space. This is balanced by lymphatic drainage so that the interstitial volume is maintained. In theory, any increase of fluid flow into the interstitium would lead to an increase in interstitial fluid hydrostatic pressure and a decrease, by dilution, of the interstitial oncotic pressure. This alteration in pressure gradients would act to limit the development of excessive interstitial fluid volumes.
The Endothelial Glycocalyx

Several experiments have demonstrated that Starling’s original work does not fully explain the movement of fluids and solutes across the endothelial barrier (2–4). This discrepancy is at least partly explained by the presence of a layer coating the endothelium known as the endothelial glycocalyx. This layer is made up of a meshwork of membrane bound, negatively charged glycoproteins, and proteoglycans. Electron microscopy has shown this layer to be between .5 and 3 μm in depth, greater than the dimension of the endothelium itself. The glycocalyx contains various proteins synthesized by endothelial cells or entrapped from the plasma. It is a dynamic structure undergoing constant enzymatic degradation and resynthesis.

The endothelial glycocalyx acts as a barrier to the passage of larger molecules through to the endothelium and is probably the primary generator of the oncotic pressure gradient between intravascular and interstitial fluids rather than the endothelial cell layer itself. In addition, it acts to prevent the adhesion of proinflammatory agents such as neutrophils to the endothelial cell layer and thus prevent secondary increases in endothelial permeability. It follows that loss of these functions resulting from destruction of this layer would significantly affect the passage of larger molecules into the interstitial space with the potential for decrease in the osmotic pressure gradient, increases in interstitial fluid volume, and subsequent tissue edema. Several factors are known to cause denuding of the glycocalyx. Pries and colleagues undertook a meta-analysis of hemodilution studies and concluded that dilution of blood with artificial fluids led to dissolution of bound plasma proteins into the flowing blood (5). In addition to hemodilution, excessive loading of the intravascular space with colloids may also cause loss of the endothelial glycocalyx (6). This may be mediated by natriuretic peptide (7), levels of which are increased both by volume overload and cardiac surgery. Furthermore, ischemia has been demonstrated to be a powerful cause of glycocalyxal destruction. In a study by Rehm and colleagues, two major components of the glycocalyx, syndecan-1 and heparin sulphate, were measured in the arterial blood of patients undergoing cardiac surgery with cardiopulmonary bypass. There was a median 65-fold and 19-fold increase, respectively, in measured plasma levels compared with preoperative levels (8), suggesting significant degradation of the glycocalyx.

The consequence of a loss of the barrier function of the endothelial glycocalyx has been demonstrated in several studies. Rehm and colleagues showed a transient 200% increase in permeability of the guinea pig coronary vascular bed to water, albumin, and hydroxyethyl starch after enzymatic breakdown of the glycocalyx during a period of ischemia (9). Electron microscopy of rat myocardial capillaries has also confirmed significant myocardial tissue edema in the absence of the endothelial glycocalyx (10).

Thus, the endothelial glycocalyx functions, among other things, as the gatekeeper to the endothelium, and its potential destruction by various elements associated with cardiac surgery including hemodilution, inflammation, and ischemia and reperfusion, leads to increased passage of osmotically active molecules into the interstitial space and the generation of significant tissue edema. This may have consequences in all tissues, but it is of particular consequence in the myocardium, which is very sensitive to accumulation of interstitial fluid with resultant impairment of function (11).

How Much Is Enough?

Classically, calculation of requirements for fluid replacement have included estimation of the preoperative deficit resulting from fasting, intraoperative insensible losses, measured losses of blood and urine, and anticipated postoperative losses resulting from fluid shifts into a third space. This is a flawed approach.

The assumption that preoperative fasting leads to a decrease in intravascular volume is not supported by the evidence. In a study by Jacob et al., the blood and plasma volumes of 53 patients undergoing gynecological surgery were measured using a double-label technique after a 10-hour period of fasting. Measured volumes did not differ from normal values calculated based on patient age, weight, and height (12).

Whereas blood and urine losses can be easily measured, insensible fluid losses must be estimated. These estimations have been heavily influenced by the desire to avoid end-organ underperfusion and a belief that liberal fluid administration is inconsequential with excesses easily corrected by the patient’s kidneys (13). Many clinicians still calculate insensible losses from large intracavity surgery using the figure of 10 mL/kg/h based originally on the work of Shires in a landmark paper published in 1961 (14). A number of methodological flaws have been identified with Shire’s work and subsequent studies have generated very different results. Lamke and colleagues measured evaporative fluid losses from open abdominal wounds by recording changes in water vapor concentration using a closed measuring chamber. They demonstrated a loss from a large open wound of only .5 mL/kg/h, which when added to basal evaporative losses from skin gave an overall loss of no more than 1 mL/kg/h (15).

The third space is taken to be that proportion of the extracellular volume that is not in communication with the remainder of the interstitial space. Also known as the nonfunctional extracellular volume, it includes fluid in the gut and other body cavities such as the pleural and peritoneal spaces. Normally the volume of fluid in these spaces is insignificant. Surgical disruption and inflammation is thought to increase the third-space fluid volume. However, this greatly increased third-space fluid volume has
never been consistently demonstrated or accurately quantified, leading some observers to suggest that it is not clinically significant (16).

A number of studies have looked at protocolized fluid administration with measured end points such as the incidence of postoperative nausea and vomiting, pain, time to recovery of bowel function, cardiopulmonary complications, tissue oxygenation and wound healing, and duration of hospital stay (17–20). Often different fluid regimens were labeled as standard, restrictive, or liberal with no consistency between studies. Studies used different types of replacement fluids as well as different volumes and investigations were often carried out in relationship to one particular surgical procedure making generalization of results difficult. It is therefore not surprising that no clear message emerges and that an ideal formula for fluid replacement has not been arrived at.

**Target Measurement**

The formulaic approach to perioperative fluid management is flawed given the uncertainties about the physiological changes on which we estimate fluid replacement and the inconsistencies of clinical research. What, then, of adopting a different approach, that of measuring an end point and aiming for a target level consistent with an optimal clinical outcome, so-called goal-directed therapy.

Blood pressure and heart rate are poor indicators of blood volume (21). Measurements of end-organ functions such as urine output are inaccurate and late markers. Central venous and pulmonary capillary wedge pressures are significantly affected by other factors as well as intravascular volume. A landmark study by Shoemaker demonstrated significant improvements in outcomes in high-risk surgery with the use of pulmonary artery catheter measurements to guide fluid and inotrope therapy to target supranormal levels of oxygen delivery (DO2 greater than 600 mL/min/m^2) (22). This approach, however, was highly resource- and time-consuming and concerns around the use of pulmonary artery catheters in the 1990s limited the adoption of this approach.

Since this time, a number of minimally invasive technologies such as arterial pressure waveform analyzers and esophageal Doppler monitoring of blood flow through the descending aorta have allowed the clinician to measure stroke volume and use this as a target for fluid replacement. A number of studies have demonstrated improved outcomes with the use of goal-directed therapy (23–26). Optimization of fluid management is not a primary indication for transesophageal echocardiography, but direct measurements of left ventricular end diastolic diameter and cardiac output would also seem to be ideal measures of intravascular sufficiency.

It should be noted that all of these measurements allow optimization of the intravascular volume. We do not have the ability to measure changes in interstitial volume acutely. Therefore, it would seem that the best approach would be to use a goal-directed approach to measure and maintain intravascular volume together with controlled administration of fluid to compensate for urinary losses and insensible losses of 1 mL/kg/h at most, being mindful of the alterations to the endothelial glycocalyx caused by cardiac surgery and the tendency toward excessive interstitial volume and tissue edema.

**Which Fluid?**

Another facet of the fluid debate involves the relative merits of crystalloids and colloids and, furthermore, which of the colloids is superior. For cardiac surgery, the debate has taken the form of attempts to discern the optimal composition of the bypass circuit priming fluid.

Crystalloid solutions distribute through the entire extracellular space. Thus, 80% of an administered dose will end up in the interstitial space. Addition of a large volume of crystalloid fluid will lead to dilution of the osmotically active components of the plasma with a reduction in plasma oncotic pressure and further tendency toward interstitial edema. The electrolyte composition of crystalloid solutions is also important. The osmolarity should be as near to plasma as possible to avoid significant changes in overall osmolarity, which would lead to movement of water between the intra- and extracellular spaces, a notable consequence of this being red cell hemolysis with hypotonic fluids.

The daily requirement for sodium is 1–2 mmol/L. This amount is contained in 1 L of .9% saline. Infusion of excess doses of sodium will lead to further promotion of interstitial edema, particularly in the face of the endocrine response to surgical trauma, which promotes renal retention of sodium in the postoperative period through elevated levels of aldosterone and cortisol. Furthermore, the hyperchloremia generated by the administration of excessive saline containing crystalloid solutions leads to the generation of a metabolic acidosis and the potentially adverse effects on cardiac contractility, adrenoreceptor function, and coagulation.

Balanced crystalloids such as Hartmann’s solution and Plasmalyte are formulated to have an electrolyte composition closer to plasma with the addition of potassium, calcium, and, in the case of Plasmalyte, magnesium. The addition of lactate and acetate, both sources of bicarbonate, renders them pH-neutral.

The addition of mannitol to the priming solution leads to a transient diuresis, which may help to offset the effects of the crystalloid load on the interstitial space.

The benefits and side effects of the commonly used colloids, namely the hydroxyethyl starches (HES) and albumin, are more difficult to discern. The ability to maintain intravascular oncotic pressure and minimize tissue

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edema is a clear advantage. Animal studies of acute normovolemic hemodilution with Ringer’s lactate solution and HES have demonstrated a more sustained increase in stroke volume index, cardiac index, and left ventricular stroke work index in response to the hemodilution with HES. In addition, gastric mucosal pH was significantly decreased with crystalloid and electron microscopy of the left ventricular wall demonstrated structural alterations with destruction of myofilaments with Ringer’s lactate (27). Cardiopulmonary bypass with crystalloid has also been shown to lead to a significant increase in myocardial edema when compared with colloid (28). Comparisons of crystalloid and colloid pump primes have also shown significantly more postoperative cerebral dysfunction with crystalloids (29). A further potential benefit of HES is its anti-inflammatory property demonstrated in a number of animal studies (30–32).

It is well recognized that synthetic colloids impair coagulation. Schramko, in a recent article, demonstrated that both HES and gelatin impaired clot strength using thromboelastometry after cardiac surgery, even at small doses of 7 mL/kg. This was not the case when a crystalloid (Ringer’s lactate solution) was used (33). Albumin would appear to offer an advantage here. A recent study demonstrated increased postoperative transfusion requirements in patients undergoing off-pump coronary bypass surgery randomized to receive 1 L HES as compared with those receiving 1 L of albumin solution (34). A number of studies have compared HES with albumin looking at blood loss after cardiopulmonary bypass. Results have been conflicting and inconclusive. A meta-analysis of such trials concluded that postoperative blood loss was significantly lower in patients undergoing cardiopulmonary bypass exposed to albumin than HES (35). Unfortunately, five of the 16 trials included were authored by Dr. Joachim Boldt, much of whose work in this area has recently been retracted. Reanalysis and further investigation are required to reach any robust conclusion.

The second concern with regard to HESs is their effect on renal function. Histological changes have been seen in renal tissue after the use of HES and studies have demonstrated an adverse effect when compared with gelatins in patients undergoing renal transplantation and the critically ill (36,37). A study of patients undergoing coronary artery bypass grafting found a decrease in glomerular filtration rate measured at Day 3 and 5 in those patients who had received HES intraoperatively (38). In contrast, a number of other studies have shown no adverse effect on renal function with HES in the setting of renal transplantation (39) or pre-existing renal impairment (40). There is some suggestion that the newer, lower molecular weight starches are safer with regard to renal function. However, a recent Cochrane collaboration review concluded that there was insufficient evidence to support this assertion (41).

Albumin has been in use since the early 1970s as a constituent of the pump prime. In addition to its properties as a colloid, it coats the surface of the bypass circuit preventing platelet adhesion, activation, and consumption (42,43). Trials comparing albumin with crystalloid prime have been small and inconclusive. A meta-analysis of seven trials in 2004 found that albumin prime better preserved platelet count than crystalloid (44). The inclusion of two studies by Dr. Joachim Boldt again casts some doubt on the findings. The coating of bypass circuits with various biofilms to prevent platelet adhesion and the triggering of the inflammatory cascade may make the benefits of albumin superfluous. This together with its cost and lack of clearcut evidence of its superiority to synthetic colloids has limited its use in recent times.

In summary, there is, and probably never will be, a perfect fluid for perioperative volume replacement in the extracellular space during cardiac surgery. Perhaps the best approach at present lies in keeping intravascular losses to a minimum by the use of cell salvage techniques, thus keeping the requirement for additional colloid, and the attendant risks, to a minimum. Interstitial losses should be calculated based on preoperative insensible losses of .5 mL/kg with intraoperative losses of 1 mL/kg. Crystalloids should be used for replacement taking into account the crystalloid load in the pump prime. Retrograde autologous priming and early recourse to vaspressors for the maintenance of blood pressure in the short term would help to reduce crystalloid/colloid volume in the pump prime. Meanwhile, potential areas for future investigation include therapeutic strategies for the protection and rapid restoration of the endothelial glycocalyx (45).

**ELECTROLYTE MANAGEMENT**

Just as important and intimately related to fluid replacement is the requirement for balanced electrolyte management. Electrolyte disturbances are common with cardiac surgery. In a study by Polderman and colleagues, levels of sodium, potassium, calcium, magnesium, and phosphate were measured in 500 consecutive patients undergoing cardiac surgery with cardiopulmonary bypass. Despite receiving potassium and magnesium in the cardioplegia solution as well as supplemental intravenous potassium and magnesium as required intraoperatively, levels of all electrolytes decreased significantly when compared with 250 other patients admitted to the intensive care unit after other major surgical procedures. Eighty-eight percent of the cardiac patients met the criteria for clinical deficiency in one or more electrolytes as compared with 20% of control subjects (46). The study authors suggested that the mechanism for this electrolyte loss was likely to be a combination of increased urinary excretion
and intracellular shift. It should be noted that all cardiac patients received low-dose dopamine, which may have enhanced any urinary electrolyte loss.

**SODIUM**

As discussed previously, sodium administration in excess of requirements may lead to increased and prolonged interstitial volume loading in the postoperative period. However, it should be noted that a fall in plasma sodium levels intraoperatively is not uncommon. This is not normally the result of a fall in total plasma sodium, but rather a result of dilution attributable to movement of water from the intracellular space. This shift occurs in response to hyperglycemia, which in turn can occur as a result of a high glucose load in the pump prime, as part of the surgical stress response and because of reduced insulin release and effect (47). This can lead to cerebral edema. Disturbances in intraoperative sodium have been shown to be a predictor of postoperative delirium (48). Patients who are hyponatremic at the time of surgery will be at increased risk (49).

**POTASSIUM**

Potassium management is important not only for successful separation from cardiopulmonary bypass, but also to reduce the incidence of postoperative dysrhythmias. Several factors affect intraoperative levels. Plasma potassium levels fall with hypothermia-induced diuresis and increased catecholamine levels, which causes increased uptake into skeletal muscle. Potassium will shift out of cells in response to a fall in insulin levels and acidemia. All of these changes are temporary and significant intraoperative hypokalemia is rare as a result of the potassium load given with cardioplegia solution. However, use of diuretics and increased levels of aldosterone and cortisol as part of the endocrine response to surgical stress will promote renal excretion of potassium and postoperative potassium loss should be anticipated.

**CALCIUM**

Mild intraoperative hypocalcemia is common. Causes include hemodilution, binding to citrate in transfused blood, binding to albumin, and as a consequence of hypomagnesemia. Calcium is often administered during surgery to normalize levels, to act as an inotrope and vasopressor, or to protect the myocardium from the adverse effects of hyperkalemia. However, there are a number of concerns regarding some potentially adverse effects of calcium administration.

The effects of intravenous calcium on systolic and diastolic function early after separation from cardiopulmonary bypass were evaluated by DeHert and colleagues in 20 patients undergoing elective coronary artery surgery (50). There was a significant but transient (less than 10 minutes) increase in systolic function and fall in myocardial compliance suggesting diastolic dysfunction. A later study, however, looked at the effect of calcium on diastolic function post-cardiac bypass. Patients were randomized to receive calcium or placebo during separation from cardiopulmonary bypass. Diastolic function was depressed equally in both groups, suggesting that calcium had no negative effect (51).

One of the main concerns with regard to calcium administration is the potential for exacerbating the ischemia–reperfusion injury to the myocardium. There is an increase in myocardial cell calcium levels during periods of ischemia. This is the result of impairment of various energy-dependent cation pumps, including those transporting calcium from the intracellular space across the sarcoplasmic reticulum. In addition, alterations in sodium and hydrogen ion transport results in increased reverse activity of the membrane-bound sodium-calcium exchange pump, leading to further intracellular accumulation of calcium ions. Sarcoplasmic transport of calcium is further impaired by the oxidative stress resulting from the generation of reactive oxygen species at the time of reperfusion. High intracellular calcium levels lead to mitochondrial dysfunction and failure with resultant cell death. Iatrogenic elevation of extracellular calcium levels may lead to yet further influx of calcium into the myocytes and an exacerbation of this process. In addition, calcium attenuates the beta-adrenergic effects of adrenaline in postoperative cardiac surgical patients (52) and has been shown, in animal studies, to potentiate the negative inotropic effects of protamine (53). Overall, it would seem that the administration of calcium before or at the time of reperfusion offers little benefit, which cannot be gained using alternative agents, and potentially significant adverse effects.

**MAGNESIUM**

Hypomagnesemia has a number of adverse hemodynamic consequences including cardiac arrhythmias, hypertension, and coronary vasoconstriction (54). Low serum magnesium levels have been demonstrated to be a predictor of major adverse cardiac events after coronary artery bypass surgery (55).

A number of studies have demonstrated the benefit of intraoperative administration of magnesium in the prevention of postoperative arrhythmias (56,57). Supplemental magnesium has also been shown to improve short-term, postoperative neurological function after cardiac surgery and may have a significant opioid-sparing effect in the treatment of postoperative pain (58).
Magnesium may be of benefit in attenuating myocardial reperfusion injury by blocking calcium ingress and by acting as a free radical scavenger (59). Most of the work in this area has been with regard to the treatment of myocardial infarction. A number of animal studies have demonstrated reduction in infarct size when magnesium is administered before reperfusion (60,61). The timing of magnesium administration appears to be important with no benefit gained when magnesium was administered even a short period after reperfusion of ischemic myocardium (62,63). The LIMIT 2 Trial investigated the effect of magnesium given concurrently with thrombolysis for myocardial infarction in over 2000 cases. Investigators found a 24% reduction in 28-day mortality. The subsequent, and much larger, ISIS 4 trial failed to show any benefit. However, as a result of differences in the study protocol in this trial, thrombolytic therapy was often given before infusion of magnesium and coronary reperfusion will have occurred before the elevation in plasma magnesium levels.

One additional effect of magnesium worth noting is its inhibition of platelet function. Gries and colleagues demonstrated inhibition of platelet function and prolongation of bleeding time at 24 hours postcardiac surgery in patients receiving magnesium intraoperatively (64). It is not clear whether this translates to a clinically significant increase in postoperative blood loss after cardiac surgery. Indeed, a recent randomized, double-blind trial of 140 patients undergoing coronary artery bypass grafting demonstrated less postoperative bleeding and red cell transfusion in the group randomized to receive magnesium (65).

In summary, levels of key electrolytes commonly fall with cardiac surgery and cardiopulmonary bypass. Bypass circuit fluid should be appropriately constituted to avoid significant dilution. Close perioperative monitoring and timely correction will minimize the adverse cardiovascular effects associated with decreased plasma levels of potassium, calcium, and magnesium. There has been much interest in the adverse effects of calcium and the potential protective effects of magnesium on the ischemic myocardium. Supplemental magnesium given at the time of reperfusion may offer many advantages, although this must be weighed against the inhibitory effect on platelet function in patients held to be at increased risk of postoperative bleeding. Mild hypocalemia is unlikely to impair cardiac function and there seems to be little justification for the administration of large doses of calcium, because any benefit is likely to be outweighed by an exacerbation of reperfusion-induced myocardial dysfunction and the attenuation of the inotropic effects of catecholamines.

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