VIA MEDICA

REVIEWS

Anaesthesiology Intensive Therapy
2014, vol. 46, no 5, 342–349
ISSN 1642–5758
DOI: 10.5603/AIT.2014.0058
www.ait.viamedica.pl

# Why crystalloids will do the job in the operating room

Robert G. Hahn

*Research Unit, Södertälje Hospital, Södertälje; and the Department of Anaesthesiology, Faculty of Health Sciences, Linköping University, Linköping, Sweden*

**Abstract**

The current trend in anaesthesia is to choose crystalloid over colloid fluids for volume replacement in the operating room. Outcome-oriented studies and kinetic analyses have recently provided more insight into how crystalloid infusions should be managed.

These fluids have a much better short-term effect on the plasma volume than previously believed. Their efficiency (i.e. the plasma volume expansion divided by the infused volume) is 50–80% as long as an infusion continues, while this fraction increases to 100% when the arterial pressure has dropped. Elimination is very slow during surgery, and amounts to only 10% of that recorded in conscious volunteers. Capillary refill further reduces the need for crystalloid fluid when bleeding occurs. These four factors limit the need for large volumes of crystalloid fluid during surgery.

Adverse effects associated with crystalloid fluids mainly include prolonged gastrointestinal recovery time, which occurs when > 3 L has been infused. Clinicians who do not want to prolong the length of the hospital stay by 1–2 days due to such problems may use colloid fluid selectively, but calculations show that the therapeutic window for colloids is quite narrow.

Inflammation is likely to decrease the fluid efficiency of colloid fluids, while its effect on crystalloids is unclear. However, some recent evidence suggests that inflammation accelerates the turnover of crystalloid fluid as well.

**Key words:** crystalloid fluids; fluid therapy, intravenous; plasma volume expansion

Anaesthesiology Intensive Therapy 2014, vol. 46, no 5, 342–349

The debate about which infusion fluid to use has recently been intensified due to the findings of kidney injury in patients receiving hydroxyethyl starch in the intensive care. Meta-analyses do not support that such a risk exists when starch is used in the operating room [1–3], but the number of patients included in these meta-analyses is still fairly small.

The anaesthetist who is concerned about what could be revealed in larger studies might be looking for the possibility of using only crystalloids in the operating room. Is this feasible? There are many reasons why this is an option. The most important one is that many beliefs about how crystalloid fluid behaves in the body are flawed.

## CURRENT VIEW OF THE PHYSIOLOGY OF CRYSTALLOIDS

The information about crystalloid fluids found in medical textbooks holds that they expand the plasma by 20% of the infused volume. No exceptions or time frame are typically mentioned. This view is perfectly logical, since the plasma volume makes up 20% of the extracellular fluid space. The distribution of fluid from the plasma across the capillary wall, based on microcirculatory studies, also seems to occur very fast so as to be completed almost immediately.

## THE KINETIC APPROACH

A more dynamic view of how the body handles crystalloid fluid can be obtained from volume kinetic studies, of which about 50 have been published [4]. Here, kinetic models that reflect our whole-body physiology in a reasonably accurate way are fitted to serial measurements of the blood haemoglobin (Hb) concentration and, possibly, the urinary excretion (Fig. 1).

Volume kinetics rests on very few assumptions, in addition to those inherent in the model. One such assumption is that the Hb molecules are evenly distributed in a well-defined but expandable body fluid volume, on average, during a fluid experiment. However, the analyses do not assume the existence of a blood volume *per se*.

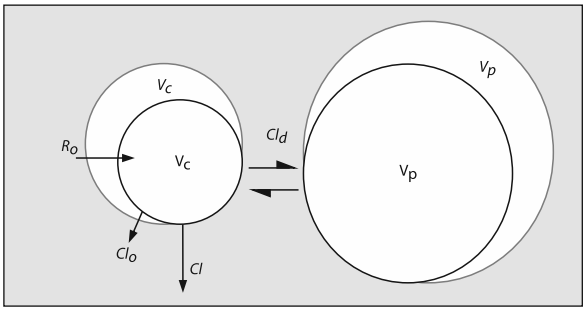


**Figure 1.** Kinetic model for analysis of the distribution and elimination of crystalloid infusion fluids. Fluid is infused at a rate of $R_o$ into a central body fluid space ($V_c$), which expands the space to a larger volume, *vc*. Elimination occurs by evaporation and baseline diuresis, $Cl_o$ (usually pre-set to 0.4 mL min$^{-1}$), and a dilution-dependent mechanism, *Cl* (elimination clearance). Distribution of fluid to a peripheral space, $V_p$, is governed by an inter-compartmental clearance constant, $Cl_d$

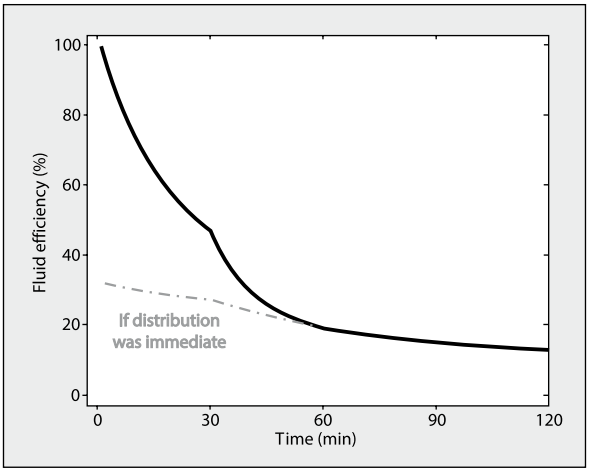


**Figure 2.** The proportion of infused crystalloid fluid that remains in the bloodstream (fluid efficiency) during and after a 30-min infusion of Ringer´s acetate. The distribution effect boosts the efficiency to much higher values than the usually proposed 20%, but only as long as the infusion continues, and for 30 minutes thereafter. Adapted from [18]

An important insight is that volume kinetics provides information about the body fluid volumes that become expanded by infused fluid. No direct information is obtained about the physiological spaces that radioactive tracers indicate. Nevertheless, the size of the central body fluid space expanded by crystalloid fluid ($V_c$) typically ranges between 2.5 and 4 L, which corresponds well with the expected size of the plasma volume.

## SLOW DISTRIBUTION

Volume kinetics studies show consistently that crystalloids are more effective plasma volume expanders than commonly believed. The most important reason is that the distribution of the fluid from the plasma to the interstitium requires quite some time when the whole body is considered. This distribution half-life is about eight minutes, both in conscious volunteers [5] and during surgery [6, 7].

The equilibration of infused fluid between the plasma and the interstitial fluid requires 30 minutes to be completed, since the process is virtually complete after four half-lives. As long as a crystalloid infusion is ongoing, the efficiency (fluid retained in plasma divided by the infused volume) is usually 50–80%. When the infusion is turned off, the plasma volume expansion quickly subsides (Fig. 2).

It is not until 30 min after the infusion has been turned off that the plasma volume expansion is what we read about in the textbooks. It would be about 33% if no elimination occurs, but as some crystalloid fluid is excreted, the fluid efficiency usually arrives at 20%. However, this is not the situation during surgery, where a continuous infusion is typically administered.

In a paper published in 1998, the fluid efficiency of Ringer´s acetate solution was shown to average 60% during 30 transurethral resections of the prostate performed under general anaesthesia [8]. This is the likely situation during most types of surgery.

## ARRESTED DISTRIBUTION

There is only one situation in which the rate of the distribution of crystalloid fluid becomes greatly retarded, so much so that it becomes arrested. This situation occurs when the arterial pressure has suddenly dropped, which is an expected consequence of anaesthesia induction, and a fairly common event during many forms of surgery.

The explanation for this phenomenon can probably be derived solely from the Starling forces, which hold that the distribution of fluid is governed by the balance of hydrostatic and oncotic forces across the capillary membrane. When the arterial pressure decreases, the capillary hydrostatic pressure falls as well, which promotes the accumulation of infused fluid in the bloodstream.

This mechanism is quite powerful but, probably due to blunting of the sympathetic tone, occurs quite slowly when anaesthesia is induced without any accompanying infusion of fluid [9, 10]. With an ongoing crystalloid infusion, all fluid remains in the circulation as soon as the mean arterial pressure has fallen by 20%, making the fluid efficiency reach 100% (Fig. 3). Therefore, crystalloid fluid is a very effective plasma volume expander when the arterial pressure has just dropped.

The anaesthetist can count on the fact that high efficiency prevails until a new Starling equilibrium has been built up, that is, when the plasma volume has increased enough to restore the capillary hydrostatic pressure. This speed is dependent on the rate of infusion and depth of anaesthesia, but a good guess is that a very high fluid efficiency prevails for 20–30 minutes. Infusing a colloid fluid at this stage of a surgical operation is obviously of questionable benefit.

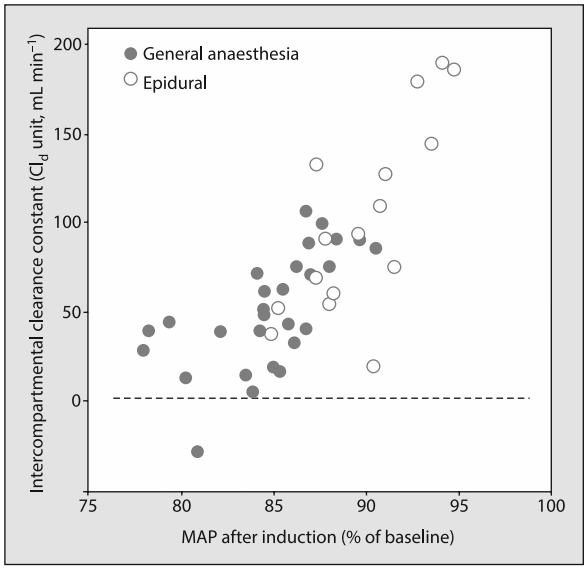


**Figure 3.** Distribution of fluid from the plasma to the interstitium decreases when the arterial pressure falls, which is usually the case during the induction of general and epidural anaesthesia. The intercompartmental clearance becomes zero when the mean arterial pressure (MAP) has fallen by 20%, which means that all infused crystalloid fluid remains in the bloodstream. Each point denotes one experiment. Data extracted from [11]

## SLOW ELIMINATION

The half-life of a crystalloid fluid in conscious volunteers is 15–25 minutes [5, 12]. However, during general anaesthesia and surgery, the half-life is about ten times longer [6, 10]. Every anaesthetist has encountered this phenomenon; after infusing 2 L of crystalloid fluid, the expected urinary excretion is 50–100 mL per hour in the operating room. A conscious volunteer would easily excrete more than 1 L during the first hour.

The reasons for this remarkable change in the elimination rate are obscure. Adrenergic receptors play a role [13], but what is probably more important is that the anaesthesia stimulates the secretion of renin and aldosterone [14]. Most crystalloid fluids contain 130–154 mmol of sodium per litre, while the kidneys are used to excreting a sodium concentration only half as high. The kidneys must then increase the sodium excretion by concentrating the urine to 400–500 mosmol kg$^{-1}$ [15]. This adaptation is more difficult in the presence of raised serum levels of aldosterone, which acts to retain sodium. However, these long-acting hormones are certainly not the only factors, as a normal elimination rate can be expected within a few hours after surgery [16].

The slow elimination certainly reduces the need for providing large amounts of crystalloid fluid in the operating room. This phenomenon also makes it questionable to indicate hypervolaemia by monitoring the urinary excretion.

## NON-EXPANDABLE INTERSTITIAL SPACES

The physiological interstitial space in an adult is about 12 L ; this volume is obtained if the researcher measures the volume with a small tracer molecule. However, only 7–8 L can be expanded by crystalloid fluid. Non-expandable parts of the interstitial space include bone tissue, the skull and the internal organs that are surrounded by tight fibrous capsules. Therefore, the interstitial space that crystalloid fluid distributes to is *not* 4–5 times larger, but *twice* as large as the plasma volume. One third of the fluid remains in the plasma and two thirds in the interstitium, provided that fluid equilibration is completed (30 minutes after ending an infusion), and there is a stable situation with regard to the Starling forces (i.e. no hypotension).

Data suggesting that 4–5 times the volume of the desired plasma volume expansion should be infused is derived from tracer studies that indicate the entire extracellular fluid space, both the parts that *can* and those that *cannot* be expanded by crystalloid fluid. Alternatively, they are obtained from volunteer studies where the elimination of crystalloid fluid is ten times faster than during anaesthesia and surgery. Finally, some studies suggesting this practice stem from the use of short-acting tracers of the plasma volume with a lack of correction for haemodilution, as well as variations in cardiac output (i.e. the transport time from the site of injection to the site of elimination).

## CAPILLARY REFILL

Three facts contribute to this author's conclusion that the rule to replace blood loss by 4–5 times as much crystalloid fluid as the bled amount is flawed. The first two have already been mentioned: the interstitial fluid space that can be expanded by fluid is smaller than that indicated by tracer substances; and secondly, that the rate of elimination of crystalloid fluid is quite a bit slower during surgery than in volunteers.

The third reason is that full replacement is not needed because a process called *capillary refill* replaces parts of the lost blood volume with fluid from the interstitial space. Unfortunately, there is some uncertainty with regard to the effectiveness of capillary refill in the operating room because the sympathetic system, which recruits the fluid by constricting the pre-capillary sphincters, may be blunted by the general anaesthesia.

The capillary refill process follows a two-phase exponential function. The early compensation occurs quickly, governed by a hydrostatic pressure gradient, while a later phase (> 1 hour) occurs more slowly due to the concentrating effect of capillary refill on the interstitial colloid pressure [17]. For this necessity of protein redistribution, the entire endogenous process of restoring the blood volume is not completed until the next day.

In conscious sheep, 35% of both hypotensive and non-hypotensive bleeding-induced hypovolaemia was restored by capillary refill within 30 minutes; this occurred much more slowly when the animals were anaesthetised with isoflurane [18].

## IMPACT ON THE PLASMA VOLUME

Figure 4 shows the impact of the distribution function and capillary refill on the plasma volume expansion from Ringer´s acetate after a haemorrhage of 900 mL in awake adult volunteers. The 3:1 rule holds that a blood loss of 900 mL should be replaced by 2.7 L of Ringer´s acetate, but our simulations show that marked hypervolaemia (+650 mL) then develops as a consequence of the therapy (Fig. 4A). In addition to being unnecessary, such vigorous infusion of crystalloid fluid in a situation of haemorrhage can increase the bleeding rate by boosting the blood flow rate [18].

Volume kinetics parameters derived from the situation when 900 mL of blood has been withdrawn from conscious volunteers can be used to simulate the infusion strategy that will prevent hypervolaemia in this setting [5]. If crystalloid fluid loading is initiated immediately after the blood loss, the recommended strategy would be to infuse 1.5 times the bled volume over 30 min, and then turn down the rate by 50% every half hour until the situation is under complete control. If the fluid therapy is initiated with a delay of 45 minutes after the haemorrhage, this would be enough to replace the blood loss in the proportion 1:1, and then to use the rates of infusion indicated above (Fig. 4B). The cautious strategy to replace a haemorrhage with only 1.5 times the bled amount with crystalloids receives support from a volunteer study where the volume effect was indicated by multiple physiological methods [19].

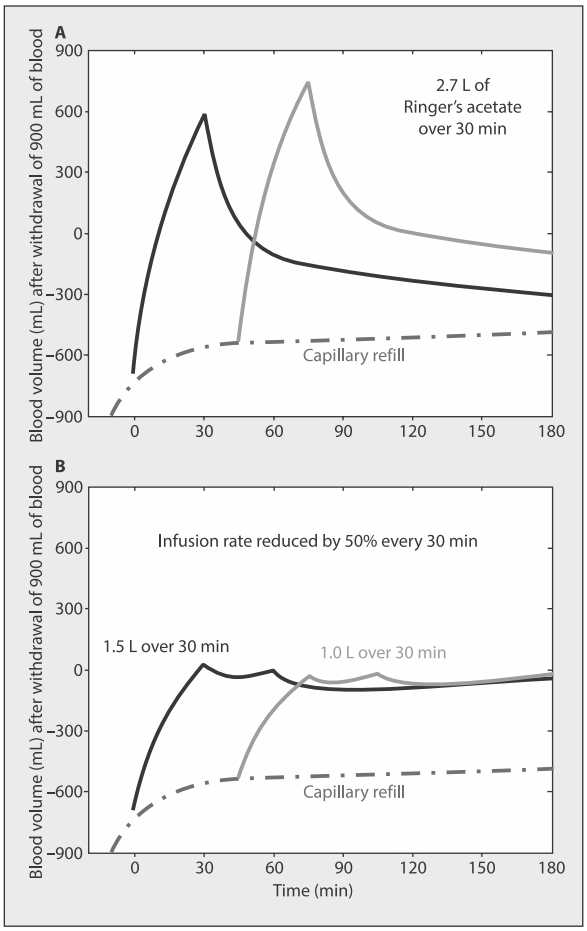


**Figure 4. A** — plasma volume when Ringer´s acetate solution is infused according to the 3:1 rule over 30 minutes, after 900 mL of blood has been withdrawn from male volunteers; **B** — to reach normovolaemia, a smaller amount of Ringer's should be infused. Titration is necessary to maintain normovolaemia. Simulations based on kinetic data from ten volunteers. Figure from [18]

Capillary refill probably makes it sufficient to replace blood loss with twice the bled amount with crystalloid fluid when patients have an intact sympathetic tone (i.e. are conscious). However, since it is unclear how effectively the capillary refill mechanism operates during anaesthesia, it might still be true that the amount of infused crystalloid fluid should finally be three times the haemorrhaged volume in that setting. This author emphasises the importance of titration to avoid hypervolaemia during ongoing surgery, and that one third of the fluid volume is saved until the early postoperative period when a possible fluid overload is more easily excreted.

## LIMITED USE OF COLLOID FLUIDS

The use of large amounts of crystalloid fluid is not without problems. Studies of the so-called 'restrictive fluid therapy' show that > 3 L of crystalloid electrolyte solution given during the day of surgery prolong the postoperative gastrointestinal recovery time by 1–2 days [20, 21]. A few more L increases the risk of pulmonary oedema and surgical infection [22]. Additionally, an infusion of 10 L is associated with a risk of fatal pulmonary oedema, which can occur several days after the surgery [23].

Although these findings are not consistent [24, 25], the anaesthetist may still want to use a colloid fluid in case surgical haemorrhage occurs, and then in the smallest necessary amount, and in as few patients as possible.

The question then is: in which situations is it appropriate to give a colloid?

Before answering this question, the decision to avoid the downsides of crystalloids by accepting the limited use of colloids must be weighed against the known adverse effects of colloids. Although they do not seem to prolong gastrointestinal recovery, they may cause allergic reactions, which do not occur with crystalloids. Colloid fluids also impair coagulation, which is mostly due to the dilution of coagulation proteins. Crystalloids also impair coagulation, but only at more pronounced degrees of haemodilution.

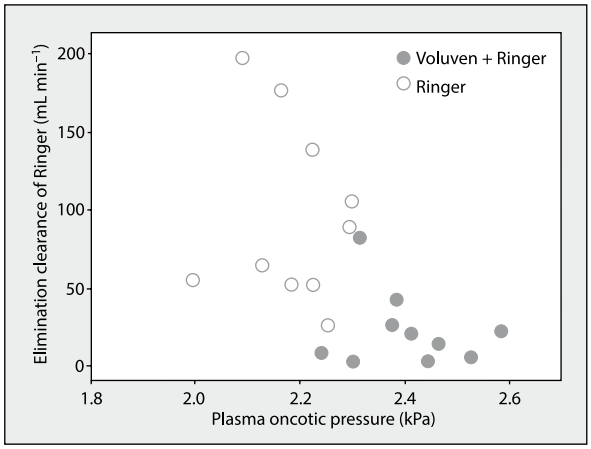


**Figure 5.** The elimination clearance of Ringer´s acetate solution becomes reduced when the plasma oncotic pressure increases, which is the case when hydroxyethyl starch (Voluven) is infused. One point is one experiment. Oncotic pressure is the mean of 5–7 measurements, s, during the experiments. Unpublished data from [31]

Initially, they actually strengthen the coagulation [26, 27]. Whether or not one specific colloid, hydroxyethyl starch, is toxic to the kidneys of relatively healthy patients is still open to question.

Finally, there is a risk that the raised colloid osmotic pressure decreases the rate of elimination of crystalloid fluid, the reason being that the glomerular filtration rate is primarily governed by a balance between the hydrostatic and oncotic pressures within the glomerular capillaries (Fig. 5). The opposing pressures are of low dignity; the oncotic pressure of the primary urine is zero, and the hydrostatic pressure in the Bowman's capsule is only one third as high as that of the glomerulus. Therefore, raising the capillary oncotic pressure might disturb this balance, and the situation is particularly sensitive if the hydrostatic pressure is low.

## THERAPEUTIC WINDOW FOR COLLOIDS

A simple computer simulation was performed in which a patient weighing 75 kg was operated on for two hours. A bolus of 500 mL of Ringer´s acetate was given during induction of anaesthesia to prevent preoperative undetected hypovolaemia, which is rare but dangerous. During surgery, the same fluid was infused at a very low rate, 2 mL $kg^{-1}$, to replace evaporation and basal diuresis.

The target Hb concentration ($Hb_n$) was set to 90 g $L^{-1}$, which means that a surgical haemorrhage can be replaced with clear fluids until this concentration is reached. The allowable blood loss for various preoperative Hb levels ($Hb_o$) was then calculated by using the equation devised by Bourke and Smith [28]:

$$\text{Allowable blood loss} = BV_o\,[\ln Hb_o - \ln (Hb_n)]$$

This equation depicts how much blood can be lost before the blood Hb level has decreased from $Hb_o$ to $Hb_n$ when the blood volume is maintained at $BV_o$. Constant normovolaemia is assumed, which means that all blood losses are replaced by an appropriate amount of crystalloid fluid. For practical purposes, $BV_o$ can be set to 7% of the body weight.

The equation should be applied with some caution, since the anaesthesia-induced reduction of the arterial pressure causes excessive retention of the crystalloid given early, which reduces the Hb concentration, regardless of blood loss. A decrease in the systolic arterial pressure of 30% [9], or in the mean arterial pressure of 20% (Fig. 3), causes a 10% decrease in $Hb_o$ in response to 500 mL of Ringer´s acetate.

Changing the body position from sitting to lying decreases the Hb level by 5–7 g $L^{-1}$ over a period of 20–40 min. Therefore, it is important to know what body position the patient was in when the preoperative Hb sample was taken.

My calculation of the therapeutic window for colloid fluid during general surgery assumes that the bled volume is replaced by three times the volume of Ringer´s, and that a 20% reduction in the mean arterial pressure is a typical reaction to the induction of general anaesthesia. The result is shown in Figure 6, and illustrates that colloid fluid has a place only when the preoperative blood Hb concentration exceeds 110 g $L^{-1}$. The limit of 6 L of crystalloid, which is associated with an increased risk of pulmonary oedema and pneumonia, can be hit only when the preoperative Hb concentration exceeds 130 g $L^{-1}$. If not, erythrocytes should be used to replace any haemorrhage that exceeds the 'allowable volume'.

Two reservations must be made with regard to Figure 6. As already pointed out, the marked distribution

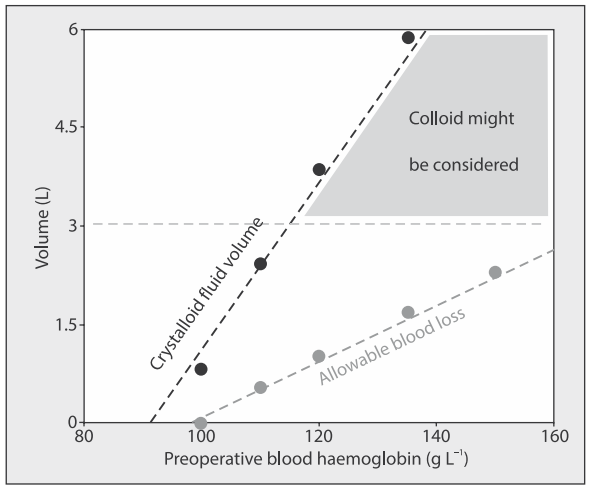


**Figure 6.** Graph illustrating the therapeutic window for colloid fluid during surgery. The calculations are based on the assumption that the blood loss is replaced by three times the surgical haemorrhage. The gastrointestinal recovery time is prolonged when the crystalloid fluid volume exceeds 3 L

function for crystalloid makes it wise to replace the bled amount with titrated amounts and, during surgery, with no more than twice the bled volume of Ringer´s. The last third can be saved for the early postoperative period. If volume compensation was given after some delay and, in particular if the patient is conscious, the last third can probably be discarded. Vigorous infusion should generally be avoided, and is only indicated in haemorrhage that causes severely compromised haemodynamics.

The second reservation is that the transfusion of plasma is associated with more adverse effects than conventional colloid fluids, and should not be used as a replacement for colloids. Therefore, the only indication for plasma is still a need for coagulation factors. Plasma also has a more variable plasma volume expanding effect than albumin 5%, which is probably due to immunological reactions [29].

## COLLOIDS AND INFLAMMATION

Inflammation increases the capillary permeability and, thereby, the transcapillary escape rate of macromolecules such as albumin. This increase can apparently be very great. For example, the rate of albumin leakage might be quadrupled in septic shock [30]. As the course of the intravascular plasma volume expansion from albumin 5% is governed mainly by the capillary leak of albumin [29], one could expect that the time course of the plasma volume expansion would last for a shorter time in inflammatory states, perhaps even being similar to that of crystalloid solutions. Unfortunately, there is no data on the duration of the plasma volume expansion of colloid fluids in inflammatory states.

In healthy volunteers, the half-life of the plasma volume expansion is 120 min when hydroxyethyl starch 130/0.4 is infused [31], while it is somewhat longer for albumin 5% [29]. This author speculates that the half-life might be as short as 30–60 min in severe inflammation, which is then in agreement with the increased capillary escape rate of albumin [30].

## CRYSTALLOIDS AND INFLAMMATION

A good question is whether the half-life of crystalloid fluid is also affected by inflammation. There is fairly good evidence that this is the case.

Pre-eclampsia is a disease of pregnancy that has an inflammatory component, although not as apparent as in sepsis [32]. Drobin and Hahn found that the distribution and elimination of Ringer´s acetate occurred twice as fast in women with pre-eclampsia than in matched pregnant controls [33].

Albuminuria is one of the hallmarks of inflammation. Data extracted from a study of the preoperative fluid turnover in 30 patients scheduled for open major abdominal surgery [34] showed that patients with albuminuria > 1 mg per mmol of creatinine had twice as high fluid clearance compared to those with no or only minor albuminuria (Fig. 7). The difference between the groups was statistically significant by $P < 0.025$ (Mann-Whitney´s test).

## REPEATED INFUSIONS

Studies in microcirculation suggest that vigorous volume loading increases the capillary permeability by breaking down the endothelial glycocalyx layer [35]. The mechanism is said to be a release of natriuretic peptides from the heart in response to the stretching of the atrial myocardium. The recommendation is, therefore, to

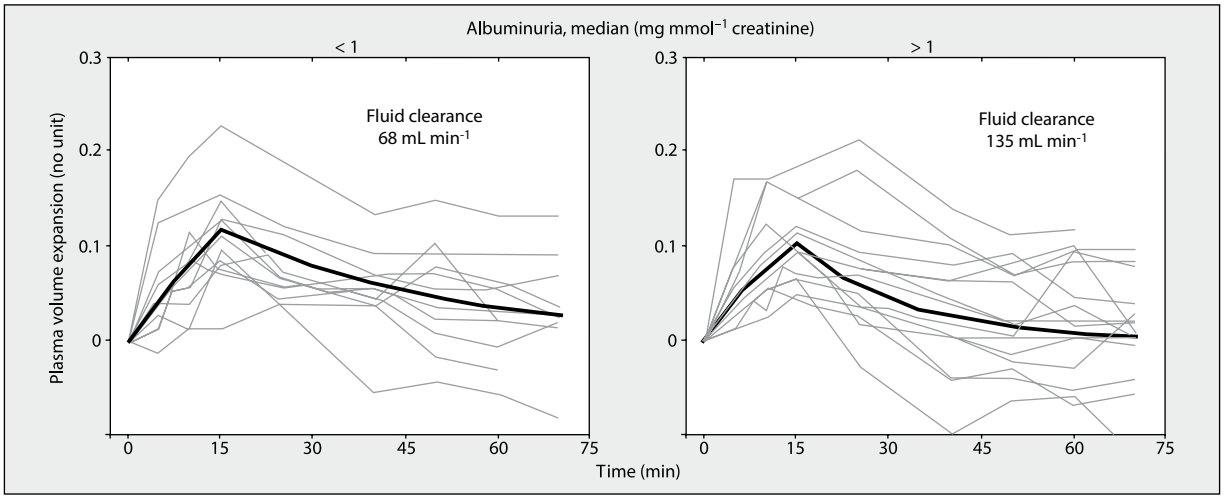


**Figure 7.** Plasma dilution in 30 patients who received 5 mL kg$^{-1}$ of Ringer´s acetate over 15 min, before major open abdominal surgery. A one-volume kinetic model showed a significantly higher fluid elimination clearance (median) in patients who excreted albumin as a sign of glycocalyx breakdown in the kidneys. Individual dilution-time curves are indicated by thin lines, and the modelled average by one thick line. Based on data from [34]

avoid hypervolaemia. How important is this mechanism in whole-body man?

In my laboratory, we have measured the brain natriuretic peptide concentration in the plasma and found no increase after infusing 5 mL kg$^{-1}$ and 10 mL kg$^{-1}$ over 15 min in volunteers (unpublished results). However, the peptide concentration doubled after infusing 25 mL kg$^{-1}$ of isotonic saline over 20 min [14]. This shows that quite vigorous crystalloid fluid loading is needed to stimulate the release of atrial natriuretic peptides.

Let us go back to previous publications and re-analyse volunteer material from 1999 to elucidate how much the turnover of Ringer´s acetate is affected by a previous fluid load large enough to stimulate the release of atrial natriuretic peptides [36]. Ten male volunteers received four intravenous infusions of Ringer´s acetate solution. On one occasion, 25 mL kg$^{-1}$ of fluid was provided over 15 min and, four hours later, the same volume over 30 minutes. On a second occasion, at least seven days later, the volunteers received the same volumes of fluid, but in the reverse order.

Volume kinetic analysis was performed of the Hb-dilution curves and the urinary excretion, using a modification of the original kinetic model based on micro-constants that allowed all curves to be analysed by the same two-volume model. The plots of the results, based on the mean parameter estimates, show that distribution takes place somewhat faster but, in particular, the rate of elimination occurs faster the second time an infusion is given (Fig. 8A, B).

The differences in fluid distribution depending on whether fluid had been given previously and, after which, damage to the glycocalyx due to the release of natriuretic peptides is likely, is apparent during or shortly after the infusions. In this study, the acceleration of the fluid elimination amounted to 10–25% (Fig. 8C).

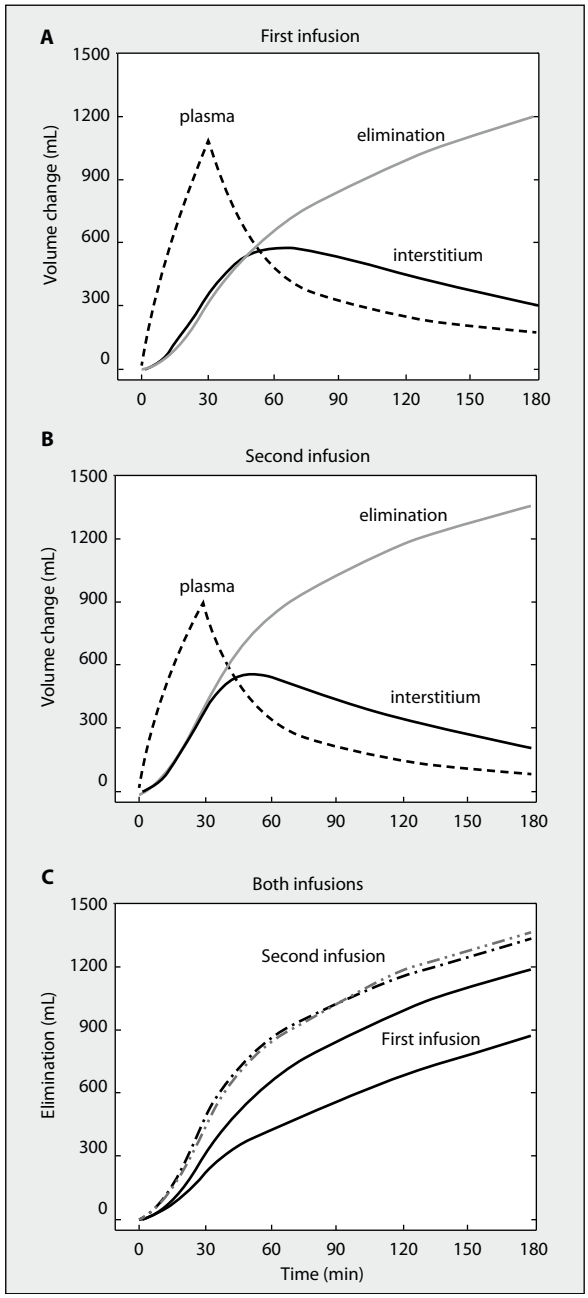


**Figure 8.** The effect of hypervolaemia-induced glycocalyx breakdown on crystalloid fluid distribution and elimination. Plots are based on mean volume kinetic parameter estimates from 40 volume kinetic experiments performed in ten male volunteers. Ten volunteers received four infusions of 25 mL kg$^{-1}$ over 15 or 30 min in randomised order on two occasions. The second infusion was given four hours after the first one. Both were brisk enough to double the release of brain natriuretic peptide; **A, B** — volume distribution of all 20 first and second infusions, respectively; **C** — elimination of the first (solid lines) and second (irregular lines) infusions. Re-calculation of data from [36]

## CONCLUSIONS

1. Several findings about how crystalloid fluid behaves during anaesthesia and surgery contribute to the fact that there are more effective plasma volume expanders than previously believed. There is no reason to use a colloid to compensate for vasodilatation when anaesthesia is induced, as the infused crystalloid is completely retained in the plasma in that setting.
2. Rapid infusion of a crystalloid to compensate for surgical haemorrhage easily leads to hypervolaemia due to the distribution effect of the crystalloids. The recommended strategy is a smooth compensation, where a third of the indicated volume is given immediately, the second 1third is infused more slowly, while the last third is saved for the end of surgery or the early postoperative period. Spontaneous capillary refill makes the last portion unnecessary if the volume compensation is started with the patient being in the conscious state, in particular if therapy is initiated with a delay after the haemorrhage.
3. Calculations show that the therapeutic window for colloid fluid is quite narrow before erythrocytes become indicated. Little is known about the impact of inflam-

mation on the efficiency of infusion fluids, but some evidence suggests that it accelerates the turnover of both colloids and crystalloids.

**References:**


1. *Martin C, Jacob M, Vicaut E, Guldet B, van Aken H, Kurz A:* Effect of waxy maize-derived hydroxyethylo starch 130/0.4 on renal function in surgical patients. Anesthesiology 2013; 118: 387–394.
2. *Van Der Linden P, James M, Mythen M, Weiskopf RB:* Safety of modern starches used during surgery. Anesth Analg 2013; 116: 35–48.
3. *Gilles MA, Habicher M, Jhanji S et al.:* Incidence of postoperative death and acute kidney injury associated with i.v. 6% hydroxyethyl starch use: systematic review and meta-analysis. Br J Anaesth 2014; 112: 25–34.
4. *Hahn RG:* Volume kinetics of infusion fluids. Anesthesiology 2010; 113: 470–481.
5. *Drobin D, Hahn RG:* Volume kinetics of Ringer´s solution in hypovolemic volunteers. Anesthesiology 1999; 90: 81–91.
6. *Ewaldsson CA, Hahn RG:* Kinetics and extravascular retention of acetated Ringer´s solution during isoflurane and propofol anesthesia for thyroid surgery. Anesthesiology 2005; 103: 460–469.
7. *Törnudd M, Hahn RG, Zdolsek JH:* Fluid distribution kinetics during cardiopulmonary bypass. Clinics 2014; 69: 535–541.
8. *Hahn RG:* Volume effect of Ringer´s solution in the blood during general anaesthesia. Eur J Anaesthesiol 1998; 15: 427–432.
9. *Hahn RG:* Haemoglobin dilution from epidural-induced hypotension with and without fluid loading. Acta Anaesthesiol Scand 1992: 36: 241–244.
10. *Olsson J, Svensén CH, Hahn RG:* The volume kinetics of acetated Ringer´s solution during laparoscopic cholecystectomy. Anesth Analg 2004; 99: 1854–1860.
11. *Li Y, Zhu S, Hahn RG:* The kinetics of Ringer's solution in young and elderly patients during induction of general anesthesia with propofol and epidural anesthesia with ropivacaine. Acta Anaesthesiol Scand 2007; 51: 880–887.
12. *Zdolsek J, Li Y, Hahn RG:* Detection of dehydration by using volume kinetics. Anesth Analg 2012; 115: 814–822.
13. *Li Y, Zhu HB, Zheng X, Chen HJ, Shao L, Hahn RG:* Low doses of esmolol and phenylephrine act as diuretics during intravenous anesthesia. Crit Care 2012; 16: R18.
14. *Norberg Å, Hahn RG, Li H et al.:* Population volume kinetics predicts retention of 0.9% saline infused in awake and isoflurane-anesthetized volunteers. Anesthesiology 2007; 107: 24–32.
15. *Hahn RG, Drobin D:* Rapid water and slow sodium excretion of Ringer´s solution dehydrates cells. Anesth Analg 2003; 97: 1590–1594.
16. *Holte K, Hahn RG, Ravn L, Bertelsen KG, Hansen S, Kehlet H:* The influence of liberal vs. restrictive fluid management on the elimination of a postoperative intravenous fluid load. Anesthesiology 2007; 106: 75–79.
17. *Hahn RG, Brauer L, Rodhe P, Svensén CH, Prough DS:* Isoflurane inhibits compensatory intravascular volume expansion after hemorrhage in sheep. Anesth Analg 2006; 103: 350–358.
18. *Hahn RG:* Fluid therapy in uncontrolled hemorrhage — what experimental models have taught us. Acta Anaesthesiol Scand 2013; 57: 16–28.
19. *Riddez L, Hahn RG, Brismar B, Strandberg Å, Svensén C, Hedenstierna G:* Central and regional hemodynamics during acute hypovolemia and volume substitution in volunteers. Crit Care Med 1997; 25: 635–640.
20. *Varadhan KK, Lobo DN:* Symposium 3: A meta-analysis of randomised controlled trials of intravenous fluid therapy in major elective open abdominal surgery: getting the balance right. Proc Nutr Soc 2010; 69: 488–498.
21. *Wuethrich PY, Burkhard FC, Thalmann GN, Stueber F, Studer UE:* Restrictive deferred hydration combined with preemptive norepinephrine infusion during radical cystectomy reduces postoperative complications and hospitalization time. Anesthesiology 2014; 120: 365–377.
22. *Brandstrup B, Tonnesen H, Beier-Holgersen R et. al.:* Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens. A randomized assessor-blinded multicenter trial. Ann Surg 2003; 238: 641–648.
23. *Arieff AI:* Fatal postoperative pulmonary edema. Pathogenesis and literature review. Chest 1999; 115: 1371–1377.
24. *MacKay G, Fearon K, McConnachie A, Serpell MG, Molloy RG, O`Dwyer PJ:* Randomized clinical trial of the effect of postoperative intravenous fluid restriction on recovery after elective colorectal surgery. Br J Surg 2006; 93: 1469–1474.
25. *Kabon B, Akca O, Taguchi A et al.:* Supplemental intravenous crystalloid administration does not reduce the risk of surgical wound infection. Anesth Analg 2005; 101: 1546–1553.
26. *Ruttmann TG, James MF, Viljoen JF:* Haemodilution induces a hypercoagulable state. Br J Anaesth 1996; 76: 412–414.
27. *Ruttmann TG, James MF, Finlayson J:* Effects on coagulation of intravenous crystalloid or colloid in patients undergoing peripheral vascular surgery. Br J Anaesth 2002; 89: 226–230.
28. *Bourke DL, Smith TC:* Estimating allowable hemodilution. Anesthesiology 1974; 41: 609–612.
29. *Hedin A, Hahn RG:* Volume expansion and plasma protein clearance during intravenous infusion of 5% albumin and autologous plasma. Clin Sci 2005; 106: 217–224.
30. *Fleck A, Raines G, Hawker F et al.:* Increased vascular permeability: a major cause of hypoalbuminaemia in disease and injury. Lancet 1985; 1: 781–784.
31. *Hahn RG, Bergek C, Gebäck T, Zdolsek J:* Interactions between the volume effects of hydroxyethyl starch 130/0.4 and Ringer´s acetate. Crit Care 2013; 17: R104.
32. *Ramma W, Ahmed A:* Is inflammation the cause of pre-eclampsia? Biochem Soc Trans 2011; 39: 1619–1627.
33. *Drobin RG, Hahn RG:* Distribution and elimination of crystalloid fluid in pre-eclampsia. Clin Sci 2004; 106: 307–313.
34. *Hahn RG, Bahlmann H, Nilsson L:* Dehydration and fluid volume kinetics before major open abdomional surgery. Acta Anaesthesiol Scand 2014; 58: 1258–1266.
35. *Woodcock TE, Woodcock TM:* Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. Br J Anaesth 2012; 108: 384–394.
36. *Svensén C, Drobin D, Olsson, J, Hahn RG:* Stability of the interstitial matrix after crystalloid fluid loading studied by volume kinetic analysis. Br J Anaesth 1999: 82: 496–502.



**Corresponding author:**

*Robert G. Hahn, MD, PhD*
*Professor of Anaesthesiology & Intensive Care*
*Research Unit, Södertälje Hospital*
*152 86 Södertälje, Sweden*
*Tel. +46 7395660972*
*e-mail: r.hahn@telia.com*
*Robert.hahn@sodertaljesjukhus.se*



*Received: 14.09.2014*
*Accepted: 26.10.2014*