

REVIEW

The half-life of infusion fluids

An educational review

Robert G. Hahn and Gordon Lyons

An understanding of the half-life ($T_{1/2}$) of infused fluids can help prevent iatrogenic problems such as volume overload and postoperative interstitial oedema. Simulations show that a prolongation of the $T_{1/2}$ for crystalloid fluid increases the plasma volume and promotes accumulation of fluid in the interstitial fluid space. The $T_{1/2}$ for crystalloids is usually 20 to 40 min in conscious humans but might extend to 80 min or longer in the presence of preoperative stress, dehydration, blood loss of $<1\text{ l}$ or pregnancy.

The longest $T_{1/2}$ measured amounts to between 3 and 8 h and occurs during surgery and general anaesthesia with mechanical ventilation. This situation lasts as long as the anaesthesia. The mechanisms for the long $T_{1/2}$ are only partly understood, but involve adrenergic receptors and increased

renin and aldosterone release. In contrast, the $T_{1/2}$ during the postoperative period is usually short, about 15 to 20 min, at least in response to new fluid.

The commonly used colloid fluids have an intravascular persistence $T_{1/2}$ of 2 to 3 h, which is shortened by inflammation. The fact that the elimination $T_{1/2}$ of the infused macromolecules is 2 to 6 times longer shows that they also reside outside the bloodstream. With a colloid, fluid volume is eliminated in line with its intravascular persistence, but there is insufficient data to know if this is the same in the clinical setting.

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Introduction

Almost all but the most minor surgical procedures begin with the attachment of an intravenous infusion. It is such a routine part of clinical practice that few of us give any serious thought as to which fluid to use, or what becomes of it once it is infused. However, establishing an intravenous infusion opens the door to problems such as fluid overload. Although probably rare, the incidence of this iatrogenic complication is unknown; clinicians are reluctant to report problems of their own making. A better understanding of the influence of infused fluids on the volumes of the plasma and the interstitium, and how this can change with a physiology manipulated by different aspects of clinical management, offers a more enlightened approach to fluid therapy. Through the medium of the half-life this review intends to examine what is known about the fate of infused fluids, and the factors that limit and extend their usefulness, so as to encourage an evidence-based approach to their use.

Turnover and half-life

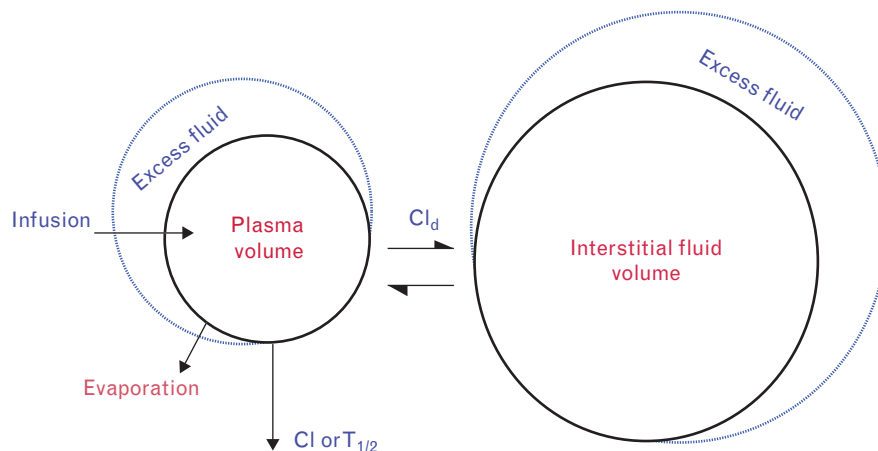
Fluids are infused to maintain, restore or elevate the circulating volume but, as plasma volume increases, water and electrolytes pass out of the circulation into the interstitium. As the volume expansion of the plasma is reversed by renal excretion, so fluid will pass back from the interstitium into the plasma, maintaining homeostasis (Fig. 1).

From a clinical perspective, the duration of plasma volume expansion, subject to both distribution clearance into the interstitium and elimination clearance by the kidneys, has an important bearing on the volume and rate of infusion of a particular fluid, and may be a significant factor in the choice of fluid. A fluid that is relatively short-lived may appear to have disadvantages in situations of plasma volume depletion such as haemorrhage, but such properties would be desirable in the event of overload. A means of comparing and contrasting the duration of different fluids is required and this is achieved through the concepts of turnover and half-life.

From the Research Unit, Södertälje Hospital, Södertälje, and Section for Anaesthesia, Linköping University, Linköping, Sweden

Correspondence to Professor Robert G. Hahn, MD, PhD, Section for Anaesthesia, Faculty of Health Sciences, Linköping University, 581 85 Linköping, Sweden
Tel: +46 739660972; e-mail: r.hahn@telia.com

Fig. 1



Schematic drawing showing the turnover of infused fluids in humans. Kinetic variables discussed in this review are marked in blue and others are indicated in red. Cl_d = distribution clearance, CL = elimination clearance, $T_{1/2}$ = elimination half-life.

To treat infusion fluids in the same manner as drugs would represent a familiar approach, but their basal constituent is water, a property they share with body fluids. The term 'turnover' is used when pharmacokinetic principles are applied to substances that are already present in the body. The elimination in a turnover model is often reported as the fractional turnover rate, but can be expressed as the more commonly used 'half-life' ($T_{1/2}$) or the time required for elimination of 50% of an infused fluid volume. A longer half-life would increase volume expansion of both the plasma and the interstitial fluid, and a reduction would have the opposite effect (Fig. 2).

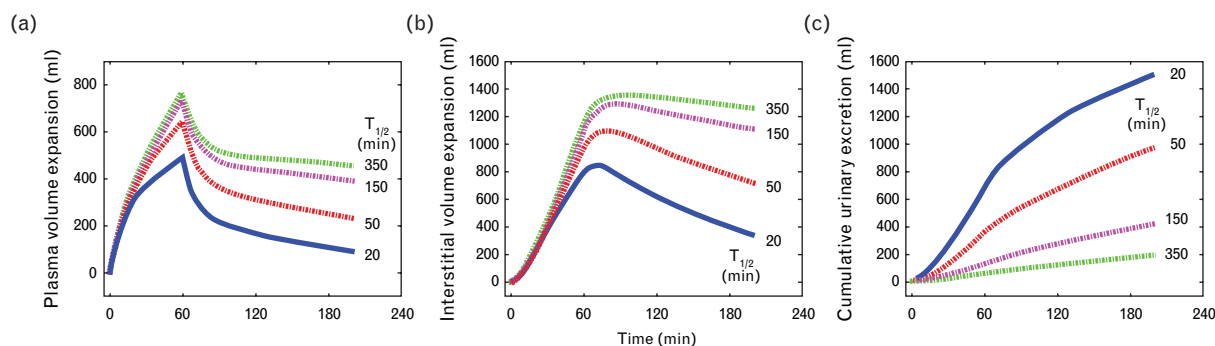
Figure 1 shows the fate of infusion fluids and also the points at which volume measurements might be made. Perhaps the simplest and easiest measure of the $T_{1/2}$ of a fluid load is the time to the first void or the voided volume at a specific time point, since urinary excretion is the ultimate fate of infused fluid. The most difficult volume

to measure is that of the interstitium, which would need an ionic isotope dilution assay and an isotopic measurement of blood volume. In between is measurement of the plasma volume, which is probably what is of greatest interest to most clinicians. Urine volume measurement and techniques for assessing plasma volume are not mutually exclusive and are worthy of further consideration.

Measuring half-life

Although urine elimination half-life is simple, it is not a very precise measure because it typically provides just one point of measurement. The time to first void is even worse, as the bladder size differs between individuals, making it no more than a rough estimate. The information it provides is largely to do with elimination, which is important in relation to overload, rather than distribution, which is related to circulating volume. However,

Fig. 2



Effects of different elimination half-lives ($T_{1/2}$) on the distribution of excess volume between plasma (a), interstitial fluid (b), and urine (c) when 2 l of Ringer's acetate is infused over 60 min. The other kinetic variables were set to typical values in conscious adult male volunteers.³⁻⁶

if the urinary excretion is related to haemodilution over time, the measure is much improved.

A variety of techniques have been used to measure plasma volume. Typically, a radioactive tracer would be injected and its dilution measured. Such a technique is unsuitable for following the kinetics of an infused fluid because it requires a volumetric steady state, which is not a feature of a dynamic physiology (Fig. 2). For example, a labelled protein such as albumin would require a steady state for 30 to 40 min, making capture of the distribution process impossible. Although such tracers distribute too slowly to make an assessment of the kinetics of a crystalloid fluid a feasible proposition, they are probably useful for colloids. As with urine volume, there is one point of measurement but based on two analyses – one before the injection and one following dilution in the plasma.

Measurement of haemodilution, provided by the blood haemoglobin concentration, overcomes these problems, permitting multiple sampling, generally providing one measurement every 5 min for as long as sampling is possible and there is still some infused fluid left in the body. A favoured technique is to take triplicate samples at baseline and then measure haemoglobin concentration once every 5 to 10 min for 3 to 4 h. This provides a very detailed picture of the haemodilution process, allowing distribution to be mathematically separated from elimination. The additional measurement of urinary excretion makes it even more precise.

An alternative to measuring haemoglobin concentration is desiccation. A tube is filled with about 1 ml of blood and it is weighed precisely to several decimal places before being placed in an open heater at 100°C overnight. The following day the tube is weighed again when all water has evaporated and the water content of the original sample can then be calculated. Similar results are obtained from data using haemoglobin concentration or water because they move in a reciprocal fashion. Measuring haemoglobin is the simpler and cheaper marker to measure, while desiccation is labour intensive and requires several measurements before the water concentration can be inferred.

Volume kinetics

This describes an approach that is identical to the way that the half-life of drugs is calculated in pharmacokinetics (see Supplementary material, <http://links.lww.com/EJA/A88>). Volume kinetics is a term that describes the application of the dilution data to a mathematical model. The data are used to generate a dilution curve that is exponential in nature, but the application of a simple formula converts this to a linear form that follows the process of dilution, and this is what is used in the volume kinetics analysis. Once the data have been fitted to a kinetic model the dilution and volume expansion of the plasma can be simulated for other rates of infusion, or

sequence of infusions, not just the one in current use. The dilution and the volume expansion of the interstitial fluid space can also be simulated and analysed, which is not possible with other methods. The expected urinary excretion can also be simulated over time. The appearance of such curves is exemplified in Fig. 2.

Studies in volunteers

Much of the initial investigation of fluid volume kinetics was conducted in volunteers and based on morning experiments involving groups of conscious, healthy volunteers who would generally be given one glass of fluid to drink in the early morning to limit overnight dehydration. Intermediate-sized fluid volumes (12.5 to 25 ml kg⁻¹ of crystalloid or 10 ml kg⁻¹ of colloid fluid) would be infused over 30 min, followed by frequent assessment of haemodilution over 3 to 4 h. Observation of urinary excretion allow more accurate calculation of the kinetic constants.

Most researchers commonly employed a 30 min infusion time, but on occasion, 15 min infusion times would be used. Some experiments compared the kinetics of the same volume being infused over 15, 30, 45 and 80 min. In total, 30 min infusions are practical from many aspects, but above all, from the data obtained, they permit a good description of the distribution phase up to termination of the infusion.

Studies with crystalloids show that volunteers eliminate infused Ringer's acetate with a median $T_{1/2}$ of 20 to 40 min.^{1–3} Half-lives of 40 to 60 min^{4–7} and even longer⁸ occur, and may be because of male gender, mild dehydration and/or stress (Table 1). A sex difference is confirmed by pooled data from several studies suggesting that males usually have a longer $T_{1/2}$ than females (55 vs 27 min; Mann–Whitney U test $P < 0.01$).^{2–8} The values given reflect the median value. Interquartile ranges are given in Table 1.

The $T_{1/2}$ varies amongst different crystalloids; it is longer for isotonic saline than for acetated and lactated Ringer solutions. This was shown in 10 male volunteers whose median $T_{1/2}$ for these three fluids was 110, 56 and 50 min, respectively.⁷ The time to the first void was also twice as long for isotonic saline than for Ringer's lactate²³ and three times longer than for 5% glucose.²⁴ This difference is most probably because of renal vasoconstriction due to excess amounts of chloride ions.²⁵

For colloids, the turnover has usually been described in terms of the rate of elimination of the oncotic macromolecules. With crystalloids, the $T_{1/2}$ is usually expressed in minutes, but with colloids, this extends to hours. The $T_{1/2}$ for hydroxyethyl starch (HES) 130/0.4 in healthy volunteers²⁶ is 12 h, and 16 h in those with mild to severe renal impairment.²⁷ HES 130/0.42 had a $T_{1/2}$ of 4 to 5 h when infused repeatedly in volunteers,²⁸ and HES 200/0.5 was eliminated with a $T_{1/2}$ of 9 h during

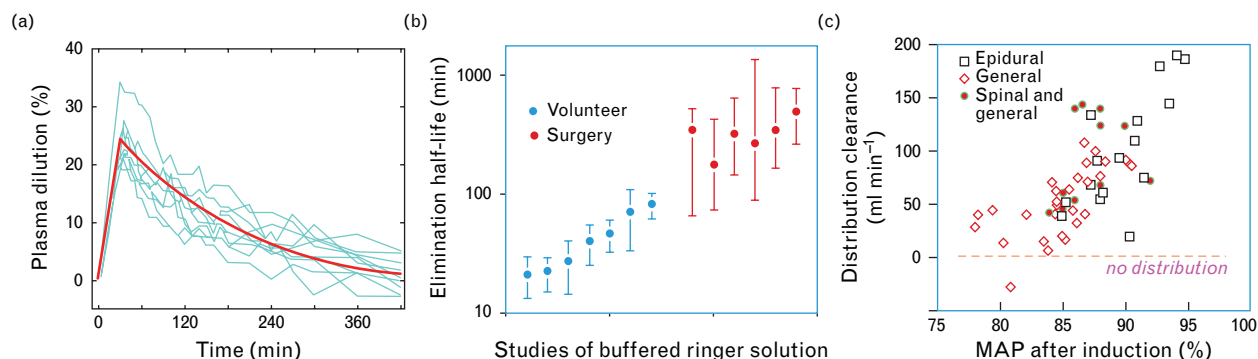
Table 1 Half-life ($T_{1/2}$) of Ringer, glucose and colloid solutions, as derived from various studies

Fluid	Study participants	$T_{1/2}$ (min)	Women/men	Reference	
Buffered ringer solution					
Acetated	Well hydrated volunteers	23 (12 to 37)	0/20	1	
	Volunteers	22 (18 to 52)	6/0	2	
	Volunteers	27 (14 to 62)	10/0	3	
	Volunteers	40 (32 to 53)	0/8	4	
	Volunteers	40 (25 to 49)	4 × 0/10	5	
	Volunteers	46 (32 to 55)	0/10	6	
	Patients 2 to 3 h before surgery	23 (8 to 61)	10/19	9	
	Dehydrated volunteers	76 (57 to 101)	0/20	1	
	Pregnancy in 34th week	71 (33 to 107)	8/0	10	
	Before caesarean section	175 (115 to 322)	10/0	11	
	Thyroid surgery; isoflurane	327 (144 to 642)	14/1	12	
	Thyroid surgery; TIVA	345 (65 to 525)	11/3	12	
	Laparoscopic cholecystectomy	268 (88 to 1368)	12/0	13	
	Lactated	Children (4 years) before surgery	30 (11 to 70)	0/14	14
		Adults just before surgery	169 (76 to 455)	8/7	14
		Open abdominal surgery	172 (75 to 424)	5/5	15
		Gynaecological laparoscopy	346 (165 to 801)	20/0	16
4 h after laparoscopy		17 (13 to 29)	15/5	17	
Glucose solution					
2.5%	Laparoscopic cholecystectomy	492 (261 to 768)	2/10	18	
	Two days after hysterectomy ^a	14 (9 to 20)	15/0	19	
	Volunteers	19 (14 to 33)	4 × 0/6	20	
5%	Volunteers	13 (13 to 22)	0/9	21	
Colloid fluids					
Dextran 70	Volunteers ^{a,b}	175 (138 to 228)	0/8	4	
HES 130/0.4	Volunteers ^a	110 (103 to 166)	2 × 0/10	8	
Albumin 5%	Volunteers ^a	110 (79 to 348)	0/15	22	
Plasma	Volunteers ^a	197 (170 to 403)	0/15	22	

Most infusions were 25 ml kg^{-1} and were infused over 30 min. $T_{1/2}$ is reported as the median and 25 to 75th percentile range. TIVA, total intravenous anesthesia. ^a Model-predicted elimination, others are based on the renal clearance. ^b Recalculated from original data with insensible fluid loss of 0.5 ml min^{-1} .

elective surgery.²⁹ A longer $T_{1/2}$ is seen with blood-derived exogenous albumin, which has a $T_{1/2}$ of 12 to 16 h,³⁰ and dextran 70 has a terminal $T_{1/2}$ of almost 3 days.³¹ It should be noted that these are elimination half-lives that do not reflect duration of plasma expansion, the key point of interest to the clinician. In fact, as might be expected, the duration of plasma

expansion is much shorter, which implies that the macromolecules persist for many hours outside the bloodstream. In volunteers, plasma volume expansion after HES 130/0.4 decays with a $T_{1/2}$ of 2 to 3 h^{4,8} (Fig. 3a, Table 1), and for 5% albumin, this rate is clearly governed by the transcapillary leakage rate of albumin molecules.²²

Fig. 3

(a) The dilution of venous plasma from infusing 10 ml kg^{-1} of hydroxyethyl starch 130/0.4 over 30 min in 10 male volunteers (thin blue lines). The modelled average (red line) extrapolated to time = 0 demonstrates a maximum peak dilution of 27%, thus the original fluid volume that became expanded was $10/0.27 = 37 \text{ ml kg}^{-1}$, or ~ 3 litres if the body weight is 80 kg. The half-life ($T_{1/2}$) can be found with reference to the slope of the elimination curve – in this case 110 minutes (See reference 8) (b) Elimination $T_{1/2}$ obtained from studies of buffered Ringer's solution. Note the log scale. (c) Distribution clearance ($C_{d,i}$) falls in relation reductions in MAP during induction of epidural, general, and combined spinal/general anaesthesia. Based on data from References 33 and 34. MAP, mean arterial pressure.

$T_{1/2}$ is a kinetic variable that changes according to the physiological situation (Fig. 2). The purpose of this review is to show that the variability in $T_{1/2}$ that results from anaesthesia and surgery, stress and dehydration, is sufficiently large to increase the risk of volume overload and long-standing tissue oedema.

Anaesthesia and surgery

General anaesthesia in isolation, without mechanical ventilation, does not affect $T_{1/2}$ provided that mean arterial pressure (MAP) is maintained, but surgery performed with general anaesthesia using mechanical ventilation is associated with marked prolongation of the $T_{1/2}$ (Fig. 3b). Twelve fasting volunteers spontaneously breathing isoflurane through a laryngeal mask had their $T_{1/2}$ for isotonic saline prolonged from 49 to 111 min, but this form of anaesthesia was associated with a drop in MAP from 85 to 55 mmHg.³² Similarly, the elimination half-life of buffered Ringer's lactate varied from 170 to 350 min during thyroid surgery¹² and open¹⁵ and laparoscopic^{13,16} abdominal surgery. Another factor in addition to hypotension that might slow down elimination during anaesthesia is marked preoperative stress.^{14,33}

With hypotension associated with spinal anaesthesia the trend is the same. During spinal anaesthesia in 10 women without hypotension, the $T_{1/2}$ for Ringer's acetate was only 17 min; for a control infusion it had been 27 min.³ But in a clinical study where spinal anaesthesia had been accompanied by a 20% drop in MAP, there was an almost four-fold prolongation of the $T_{1/2}$.³⁴

The occurrence of intraoperative fluid retention is known to all anaesthetists, who, hypothetically, might aim for an hourly urinary excretion of 50 to 100 ml after having infused 1 to 2 l of fluid. The urinary excretion would be 10 times greater in a conscious volunteer receiving the same amount of fluid. The slower turnover of crystalloids underlines the care with which such fluids should be titrated during anaesthesia and surgery. Here, the urine flow is a poor index to fluid overload. An illustration of this was given by Matot and colleagues,³⁵ where patients undergoing laparoscopic bariatric surgery were randomised to either a restrictive ($4 \text{ ml kg}^{-1} \text{ h}^{-1}$) or a liberal ($10 \text{ ml kg}^{-1} \text{ h}^{-1}$) regimen of Ringer's lactate during their procedures. The total urine output at the end of the 3 h procedures was 100 ml and 107 ml, respectively (7.5 and 3.2% of the infused volumes). The serum creatinine did not change.

Unlike crystalloids, with HES 130/0.4 the $T_{1/2}$ for plasma volume expansion during anaesthesia and surgery (without hypotension) is the same as that of the volunteers.³⁶ This was true for laparoscopic cholecystectomy,³⁷ and also for three different HES solutions during hip replacement.³⁸ Dextran 70 had a longer intravascular persistence,³⁸ with a $T_{1/2}$ of 2.5 h when assessed by plasma albumin dilution 2 h after surgery.³⁹ The $T_{1/2}$ of colloids

increases in the same manner as crystalloids when infused during anaesthesia-induced hypotension.⁴⁰ However, during hypovolaemia, in contrast to crystalloids, which show only a slightly prolonged intravascular persistence,⁶ the plasma volume expansion of colloids that results from hypovolaemia is much longer lasting. The evidence for this is taken from a study of normotensive volunteers who were given HES⁴¹ and autologous plasma⁴² to replace blood that has just been withdrawn. Urine-based data are lacking for the elimination $T_{1/2}$ of colloid fluid volumes from anaesthesia and surgery.

Understanding fluid retention during surgery

Although there is no doubt that marked fluid retention occurs during surgery, there is not a conclusive explanation for it. One hypothesis is that anaesthesia-induced vasodilatation raises the threshold for excretion by opening up more space for fluid in the bloodstream. This vasodilatation is accompanied by a reduction in the arterial pressure that, in turn, impairs renal perfusion. Evidence for this latter effect is seen in increased secretion of renin and aldosterone during experimental isoflurane anaesthesia, even when a brisk bolus of saline has been given.³² It is possible to restore some of the normal diuretic response to volume expansion by manipulation of the adrenergic receptors. Blockade of the β -1 receptors with esmolol and stimulation of the α -1 receptors with a low-dose infusion of phenylephrine ($0.01 \mu\text{g kg}^{-1} \text{ min}^{-1}$) during laparoscopic surgery, reduced the $T_{1/2}$ for lactated Ringer's from 329 min (control) to 165 and 147 min, respectively.¹⁶

The significance of prolongation of the $T_{1/2}$ might have benefits in terms of the duration of plasma expansion, but it also promotes accumulation of fluid in the interstitium. Considering the half-lives shown in table 1, the perioperative plasma volume expansion 2 h after infusing 2 l of fluid would be 3 times greater during a typical laparoscopy than in a well hydrated, conscious volunteer (Fig. 2). Accumulation of larger amounts of fluid in the interstitium breaks up the interstitial matrix and creates a high compliance situation for volume expansion, which further aggravates the oedema.^{43,44} Accordingly, intraoperative fluid overload causes a weight increase that can last several days.⁴⁵

The postoperative period

Soon after the end of the surgical procedure the normal $T_{1/2}$ for buffered Ringer's solution is restored. The turnover even shows acceleration, which probably reflects activation of the inflammatory cascade. Termination of general anaesthesia is followed by a 15 min process of spontaneous concentration of the plasma by 5 to 10%.^{13,19} Holte and coworkers illustrate this with a study of laparoscopic cholecystectomy; the $T_{1/2}$ of Ringer's lactate was just 17 min at 4 h after surgery, but had been 41 min at 1 to 5 days before.¹⁷ The reduction of the $T_{1/2}$ was the same

irrespective of whether the administration of the fluid had followed a restrictive (15 ml kg^{-1}) or liberal (40 ml kg^{-1}) protocol. Similarly, glucose 2.5% with electrolytes had a $T_{1/2}$ of several hundred minutes during surgery,¹⁸ but 2 days after hysterectomy the same fluid had a $T_{1/2}$ of only 14 min,¹⁹ which is similar to that found in healthy female volunteers.^{20,21} Urinary excretion at this time is markedly increased, but mainly in response to new fluid.

Although the above descriptions reflect the picture for elective surgery, the situation may be different in emergency and trauma surgery. Preoperative trauma probably acts to prolong the $T_{1/2}$ for fluid given in the postoperative period. Elderly patients had a $T_{1/2}$ for Ringer's acetate of 40 min 1 day after hip fracture surgery compared to 15 min in healthy age-matched controls.⁴⁶

Distribution effects

The perceived wisdom is that infused crystalloids are fairly rapidly distributed throughout the extracellular fluid. This may not be true for all situations. Two recent studies suggest that distribution of small amounts of crystalloid fluid ($\leq 5 \text{ ml kg}^{-1}$) might be limited to only within the plasma volume.^{1,9} An explanation for this is that for such small volumes, the interstitial fluid matrix has too low a compliance to permit volume expansion.^{43,44} Larger volumes clearly open up the interstitium for volume expansion.^{7,8} Crystalloids flow almost freely across the capillary membrane, but the fine proteoglycan filaments in the interstitial matrix prevent fluid from flowing easily through the gel.⁴³ The restriction of flow explains why crystalloid fluid has a distribution half-time of about 8 min, making equilibration complete in 25 to 30 min. This half-time is quite stable under variable physiological conditions, and a dramatic reduction only occurs in acute hypotension. A decrease in MAP of $>20\%$

arrests the fluid distribution until a new Starling equilibrium is reached (Fig. 3c).

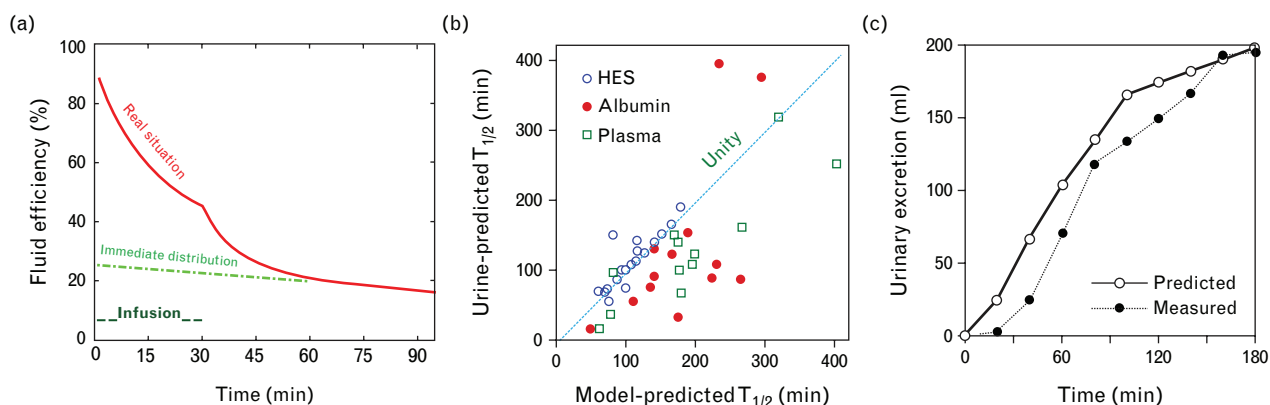
The fact that crystalloids have a relatively slow distribution in this situation greatly improves their clinical efficacy. The fluids have a reasonably good plasma volume expanding effect as long as the infusion is continued, but this effect disappears within 30 min of the infusion being turned off (Fig. 4a). Even though distribution is prolonged, the process still occurs too fast to be adequately illustrated by tracer methods.

Is the colloid volume distributed?

Distribution of colloid solutions into the interstitium is a concern because the macromolecules may have the potential to make oedema refractive. Just how much of an infused colloid fluid distributes into the interstitium under normal circumstances has not been studied in detail. A simple evaluation can be made from existing data in healthy volunteers by comparing the $T_{1/2}$ derived from the haemodilution curve (model-predicted $T_{1/2}$) with the $T_{1/2}$ obtained from urinary excretion (Fig. 4b). The two $T_{1/2}$ values are quite similar for HES. The model-predicted $T_{1/2}$ is longer for both 5% albumin and autologous plasma, which means that the urinary excretion exceeds the reduction of the plasma volume. These calculations suggest that HES does not hydrate the interstitial fluid space, while both albumin and plasma recruit fluid from the interstitium. By contrast however, there is evidence that colloid macromolecules do diffuse into the interstitium and prolong the excretion of crystalloids infused later.⁸ Whether or not this is true in the perioperative setting is not known.

The comparison between the model-predicted elimination of crystalloid fluid and the measured urinary excretion is similar. A frequent finding is that the

Fig. 4



(a) The fluid efficiency (plasma volume expansion divided by infused volume) based on kinetic data from thyroid surgery.⁵⁷ (b) Comparison between model-predicted and urine-predicted elimination $T_{1/2}$ in volunteers receiving various colloid fluids.^{8,22} (c) Model-predicted elimination of fluid appears as urine with a lag time of 15–20 min. Median values from 60 laparoscopic operations where 20 ml kg^{-1} of Ringer's lactate was infused during the first 30 min.¹⁶

model-predicted elimination is slightly larger^{32,47} than urinary excretion (Fig. 4c). This discrepancy is probably due to filtration of fluid through nonfenestrated capillaries, which can only be transported back to the plasma via a time-consuming route through the lymphatic system.⁴⁸

Inflammation

Just as anaesthesia, surgery and stress affect the rates of distribution of fluids, so too does inflammation. In the presence of sepsis the intravascular persistence of colloid fluid volumes is likely to be shortened as inflammation hastens the capillary leakage of macromolecules by breaking down the endothelial glycocalyx layer.^{48–50} Septic shock increases the capillary leakage rate of albumin by 300%,⁵¹ which probably reduces the $T_{1/2}$ for the plasma volume expansion to <1 h. Colloid fluid volume, or simultaneously infused crystalloids, will then redistribute themselves to the interstitium by virtue of the oncotic properties of the leaking macromolecules. Tissue oedema is imminent if the lymphatic system cannot catch up with this increased flow. Little is known about colloid fluid turnover in diseases with high capillary permeability; the exception is preeclampsia,⁵² where the $T_{1/2}$ is significantly reduced compared to gestation-age matched controls, 12 min v 71 min respectively.¹⁰ Pre-operative patients with minor albuminuria had a shorter $T_{1/2}$ when compared to those without albuminuria.⁵³

In severe hypervolaemia the plasma atrial natriuretic peptides concentration is raised and this has an effect similar to inflammatory mediators. Rehm, Jacobs and colleagues,^{54,55} using a double-isotope technique, reported that 1.3l of colloid fluid (HES or 5% albumin) given to normovolaemic patients expanded the plasma volume by only 40% of the infused volume. This limited volume expansion is believed to be due to hypervolaemia induced ANP resulting in rapid loss of the colloid from the circulation. However, both the methodology and the calculations used in these studies^{54,55} has been criticised.⁵⁶ Recalculation of the data does not support the contention that the volume effect of colloid is poor when given in this limited hypervolaemic state.⁵⁶

Conclusion

The turnover of crystalloid fluid shows a marked variability that is determined by the physiological condition, stress, dehydration, anaesthesia and surgery. The normal degree of variability spans at least a 10-fold variation. Although a volunteer has little problem in excreting a fluid load, the patient undergoing surgery with general anaesthesia might struggle in dealing with the same situation. Compared with conscious volunteers the long elimination $T_{1/2}$ during anaesthesia and surgery increases the plasma volume expansion even after distribution is complete. Although the diuretic response to crystalloid fluid might be much weaker during surgery, there is no

evidence that the fluid retention causes renal impairment. The result of crystalloid fluid therapy in physiological situations where the $T_{1/2}$ is very long will ultimately be long-standing interstitial oedema. This underlines the importance of careful titration of crystalloid fluid during anaesthesia and surgery.

Distribution of crystalloid fluids from the plasma to the interstitium requires 25 to 30 min for completion, enhancing their plasma volume expanding effect for the duration of the infusion, and for up to half an hour thereafter. Riding on this volume 'wave' greatly improves the clinical efficacy of crystalloid fluids.

The question of how much colloids contribute to interstitial oedema remains unknown for lack of clinical data.

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