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Volume Kinetics for Infusion Fluids

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ABSTRACT

Volume kinetics is a method used for analyzing and simulating the distribution and elimination of infusion fluids. Approximately 50 studies describe the disposition of 0.9% saline, acetated and lactated Ringer's solution, based on repeated measurements of the hemoglobin concentration and (sometimes) the urinary excretion. The slow distribution to the peripheral compartment results in a 50–75% larger plasma dilution during an infusion of crystalloid fluid than would be expected if distribution had been immediate. A drop in the arterial pressure during induction of anesthesia reduces the rate of distribution even further. The renal clearance of the infused fluid during surgery is only 10–20% when compared with that in conscious volunteers. Some of this temporary decrease can be attributed to the anesthesia and probably also to preoperative psychologic stress or dehydration. Crystalloid fluid might be allocated to "nonfunctional" fluid spaces in which it is unavailable for excretion. This amounts to approximately 20–25% during minor (thyroid) surgery.

VOLUME kinetics is an adaptation of pharmacokinetic theory that makes it possible to analyze and simulate the distribution and elimination of infusion fluids.

By the use of volume kinetics we can study the disposition of different infusion fluids in terms of parameter values or, by simulation, compare the rates of infusion required to reach a predetermined plasma volume expansion. Volume kinetics has also made it possible to quantify changes in the distribution and elimination of fluids that result from stress, hypovolemia, anesthesia, and surgery.

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Theoretical Issues

Basic Principles

As in pharmacokinetics, one has to build a theoretical model that captures the anticipated disposition of the administered substance. Blood samples for measuring its concentration are often taken repeatedly, both during and after administration. The optimal values of the model parameters are then estimated by a nonlinear least-squares regression routine that compares the measured concentrations with computer-generated data points based on the differential equations describing the model.

A difficulty in applying these principles to fluid therapy is that water is the main component of both the infusion fluids and the plasma.[1,2] Hence, the plasma concentration cannot be expressed in the usual way. However, the water content of whole blood reflects the dilution of solid elements such as hemoglobin.[3,4] Therefore, the dilution of hemoglobin may serve as an indicator of the "concentration" of an infusion fluid.

When calculating the dilution, the lowered hemoglobin concentration must be placed as the denominator of the ratio to arrive at a correct proportion between changes in hemoglobin and water volume. Hence, we should calculate the dilution of the tracer in such a way that it corresponds to the fractional volume expansion (fig. 1). Finally, the ratio is divided by (1 − hematocrit) to arrive at the dilution of the plasma, which is the body fluid that equilibrates with the interstitial fluid volume (appendix 1).

The Two-volume Model

The basic model for volume kinetics has two fluid spaces (fig. 2) and is applicable for crystalloid fluids in anesthesia and surgery, dehydration, and hypovolemia.

Fluid infused at a rate R_o increases the volume of a central body fluid space V_c to a larger volume, v_c. The rate of elimination is given by the product of the fractional volume expansion $(v_c - V_c)/V_c$ and the elimination clearance, Cl. Thus, Cl is the part of the expanded fluid volume $(v_c - V_c)$ that is totally eliminated per unit of time.

All sources of baseline fluid losses, such as the insensible water loss and baseline urinary excretion, are accounted for by a zero-order constant Cl_o, which is usually preset to 0.3–0.5 ml/min depending on the size of the subject.[5,6] The total

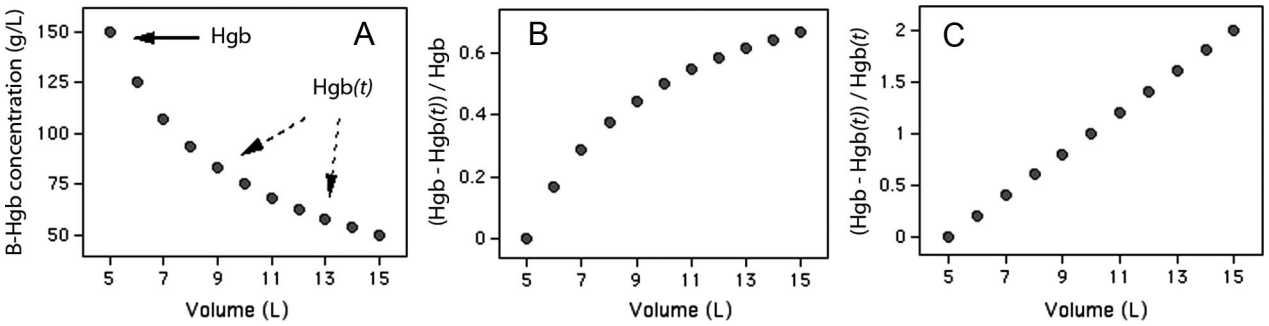

Fig. 1. The reduction in the concentration of a tracer substance (Hgb, hemoglobin) when a fixed amount of tracer is diluted by increasing amounts of water (*A*). The correct proportion between Hgb concentration and water volume cannot be obtained by placing the baseline Hgb in the denominator (*B*), but only by placing the diluted Hgb in the denominator of the ratio used to calculate dilution (*C*).

elimination clearance is $Cl + Cl_o$, which approaches Cl_o when v_c approaches V_c. If the urinary excretion is measured, Cl_o can be estimated and then indicates all fluid that may be allocated outside the kinetic system in the body (if any), plus the baseline fluid loss.

Fluid is distributed to a peripheral body fluid space, V_t, which becomes expanded to v_t. The rate of exchange between the V_c and V_t is determined by the difference in dilution between them, multiplied by the distribution clearance, Cl_d. As fluid flows freely and does not bind to tissue, Cl_d is given the same value for flow in both directions (appendix 2).

Volume kinetics differs from pharmacokinetics in several ways. For example, the infused volume is not negligible in relation to the volumes of distribution, v_c and v_t, the size of which changes constantly during an experiment (table 1). In fact, their increase is what primarily exerts a therapeutic effect in sick patients.

These differences were so far emphasized by the use of nonstandard symbols, which has caused confusion. Today, the symbols are similar to those of a compartmental model. The following parameters are equivalents: $V_c = V_1$, $V_t = V_2$, $Cl_d = k_t$, $Cl = k_r$, and $Cl_o = k_b$.

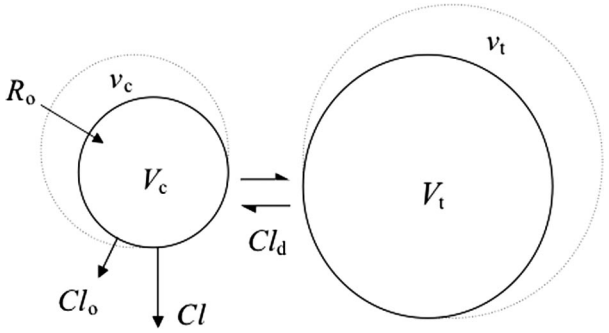

Fig. 2. The two-volume kinetic model. Fluid is infused at the rate R_o into the body fluid space V_c, which is then expanded to v_c. Fluid exchanges with V_t and becomes eliminated *via* a dilution-dependent mechanism, *Cl*. All sources of baseline fluid losses are accounted for by Cl_o. When v_c approaches V_c, the fractional increase in volume approaches zero. When this occurs, the total elimination clearance approaches Cl_o. Cl_d = distribution clearance.

Physiologic Correlates

The two-volume kinetic model is designed to suggest that V_c and V_t correspond to the plasma volume and the interstitial fluid space, respectively, and that the fractional volume expansion distributes fluid by modifying the hydrostatic and colloid pressures in these body fluid spaces. Cl_d is believed to reflect differences in perfusion and capillary permeability between body regions.[7] Because infused fluid is eliminated by the kidneys, the *Cl* estimated by the curve-fitting procedure should correspond to the renal clearance, Cl_r. However, the parameter estimates are not direct measurements of physiologic variables but rather are functional trend values that indicate how the body actually handles an infusion fluid.[7]

The size of V_c is 3–4 l, and this is close to the expected[3,7,8] or measured[9] size of the plasma volume. V_c becomes slightly larger if calculations are based on arterial hemoglobin samples rather than on venous samples.[7]

The size of V_t is 6–8 l in adult males weighing 70–80 kg and, therefore, smaller than the expected size of the interstitial fluid space.[3,10,11] In contrast to tracer ions such as bromide, however, volume kinetics indicates only the body fluid spaces that can be expanded, and this is not possible in certain body regions (such as the skeleton and the skull). Moreover, some tissues have high compliance for volume expansion whereas others require a higher fluid pressure for expansion to occur.[12] Therefore, V_t may be larger for massive fluid infusions[13] but not for the rates and volumes normally administered to humans.[14] The precision of an estimate of V_t is usually poorer than of V_c.

The One-volume Model

The plasma dilution-time profile does not always show the biexponential shape typical of the two-volume model. Instead, the curve-fit might be excellent if we assume that infused fluid distributes into a single volume only (appendix 2). This is the case for a colloid fluid such as dextran 70 in healthy volunteers.[3] The one-volume model is also appropriate for crystalloid fluid when elimination is fast, which is sometimes the case in volunteer experiments.[11,14] The rationale is that an increasing ratio Cl/Cl_d offers less time for the

Table 1. Differences in Symbolism between the Pharmacokinetic Model for Drugs and Volume Kinetics for Infusion Fluids

	Pharmacokinetic model	Volume kinetics
Modeled entity	Mass, X	Volume expansion, $(v[t] - \tilde{V})$
Unit	mg	ml
Input data	Concentration, C	Dilution, $\frac{[\text{Hgb}/\text{Hgb}(t)-1}{1-\text{Hct}}$
Unit	mg/ml	no unit
Volume of distribution	$V = \text{Dose}/C_o$	$v(t)$
Key parameters	V, Cl	V, Cl
Amount in the body	$X = V \cdot C(t)$	$v - V = \text{dilution} \cdot V$
Change in amount	$\frac{dX}{dt} = R_o - Cl \cdot C(t)$	$\frac{d(v-V)}{dt} = R_o - Cl \cdot \frac{(v(t)-V)}{V}$
Rate of elimination	$Cl \cdot C(t)$	$Cl \cdot (v(t)-V)/V$
Renal clearance, Cl_r	$\frac{\text{urinary excretion of drug}}{\text{AUC for drug in plasma}}$	$\frac{\text{urine volume}}{\text{AUC for plasma dilution}}$
Total elimination clearance	Cl	$Cl + Cl_o$

The baseline fluid losses, described by Cl_o, have been omitted except in the last definition.
AUC = area under the curve; Cl = clearance; C(t) and C_o = concentration at any time and at baseline; Hbg(t) and Hbg = hemoglobin concentration at any time t and at baseline; Hct = hematocrit at baseline; v(t) and V = expanded body fluid space at any time and at baseline.

fluid to expand V_t before elimination occurs, whereby V_c and the partially expanded V_t blend into a single fluid space of intermediate size (fig. 3).

Requirements for Successful Analysis

The fluid is best given as a brisk intravenous infusion over 30 min. For a crystalloid solution, 20–25 ml/kg is recommended because smaller volumes may give rise to "noisy" data. Blood sampling is carried out repeatedly over 3 h (sometimes 4 h). It is essential to measure hemoglobin with high precision, with a coefficient of variation close to 1%. Analyzing hemoglobin on a blood gas machine offers little chance to reach this level of precision. Accurate sampling and a high-level method of analysis are recommended to keep the between-sample variability as low as possible.

The two-volume model requires high data quality because four parameters are to be estimated (V_c, V_t, Cl, and Cl_d). If elimination is slow, the analysis will have difficulty differentiating between allocating fluid to V_t or as eliminating from the system expressed by Cl. One may then replace Cl by the renal clearance (Cl_r) as calculated from the measured urinary excretion (appendix 2).[6] On doing so, only three parameters have to be estimated by least-squares regression (V_c, V_t, and Cl_d), which increases the stability of the model. The same trick is often helpful if the sampling time is shorter than 3 h.[10]

The one-volume model is more robust as only two parameters are to be estimated (V and Cl). With crystalloid fluids, the baseline hemoglobin level should be reached within 3 h (fig. 3A), whereas colloids have a much longer elimination phase.[3,15]

Physiologic alterations should be kept small during the study period. For example, a change of body position and the termination of general anesthesia alter the hemoglobin level.[16] Drugs that cause diuresis or modify the adrenergic receptor activity may confuse the results if given when an experiment has already started.

Bleeding can be accounted for, if known (appendix 3).

Selection of Model

A statistical test, such as the F test, might be applied to help decide whether the one- or two-volume model should be applied (appendix 2). Plotting the agreement between model-predicted and -measured urinary excretion may be a helpful adjunct.

The best situation is when one is able to compare parameter estimates derived by the same model. Fortunately, the two-volume model is appropriate in the vast majority of patients undergoing surgery.[17] In contrast, the parameters for groups of healthy volunteers may be difficult to evaluate because the two-volume model is often appropriate in some subjects but not in others.[10,11,14] However, all our studies published after 2003 have given the results according to only one variant of the model. For this purpose, simplifications of the two-volume model have sometimes been used.

A modification developed by Drobin[18] deals with the absolute instead of the fractional volume expansion. The presence of V_t is acknowledged but its size is not estimated. The two-volume model then analyzes nearly all experiments, even when the urinary excretion is so large that the one-volume model would normally be appropriate.[7]

The conventional two-volume model is usually simplified in another way when the sampling time is short (<3 h). Setting V_t to a very high fixed value (like the body weight) blunts the flow from V_t to V_c which, with or without assum-

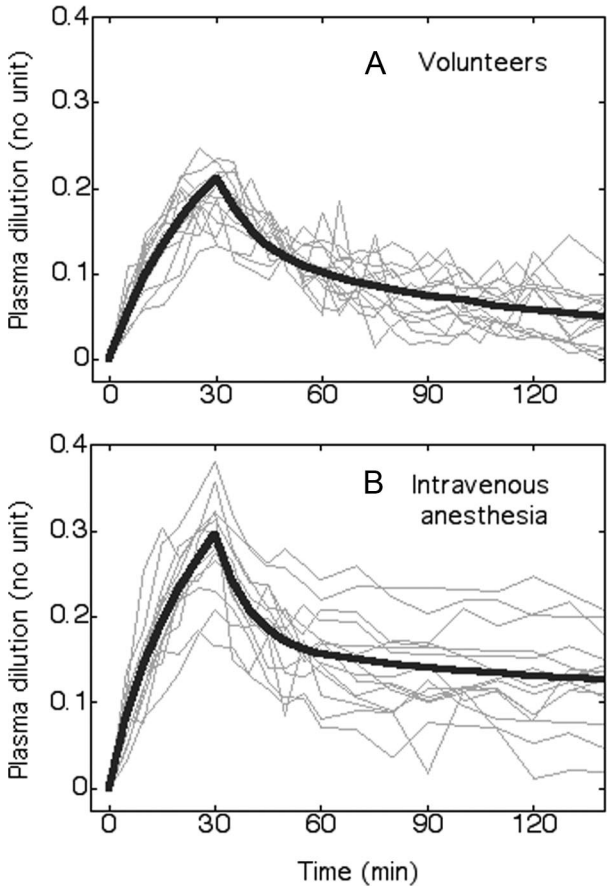

Fig. 3. Plasma dilution during and after intravenous infusion of 25 ml/kg acetated Ringer's solution over 30 min in 14 representative normovolemic volunteers (*A*, selected from Refs.[11,44]) and in 14 patients undergoing thyroid surgery with intravenous anesthesia (*B*, based on Ref.[17]). *Thin lines* = individual experiments. *Dark lines* = optimal curve fit for kinetic analysis based on all experiments.

ing that $Cl = Cl_r$, yields robust estimates of V_c and Cl_d even during shorter surgery.[16,19–21]

"Noisy data" have been handled by applying only the one-volume model to all experiments[22–24] or by pooling the data from all subjects into a single analysis[25–27] (fig. 3).

Parameter estimates may be compared only within the framework of the same model simplification.

Extensions of the Kinetic Models

In addition to population[9] and volume turnover kinetics,[28] several modifications of the two basic kinetic models have been developed to focus on issues of special interest.

The effect of the induction of anesthesia on the kinetics of infusion fluids has been studied by allowing the model to account for an abrupt change of physiology half-way through an experiment. The kinetics before and after the change in physiology may then be compared in the same patient.[20,29–31]

The models can also be slightly modified to account for the osmotic fluid shifts that occur when hypertonic fluid is infused (appendix 4). For this purpose, a three-volume model has been developed.[11,32]

One solute may be allowed to act as a driving force to distribute fluid into the intracellular space, such as is the case for glucose solutions.[33] Kinetic analyses of glucose and the fluid volume are then combined so that the uptake of glucose to the cells attracts water in proportion to the osmotic strength of the glucose molecule.[34–36] The volume change of the body cells can then be modeled.[37] As their hydration is derived from V_t, it is difficult to find any expansion of V_t as long as the Cl for glucose and fluid as well as perspiration are normal.

Although the existence of the "third space" has been questioned,[38,39] irreversible loss of fluid from the two functional fluid spaces to a third but "nonfunctional" space can be quantified by letting the computer estimate the zero-order constant Cl_o.[17] The loss might possibly represent accumulation in injured tissue and in the peritoneal and gastrointestinal cavities, as well as perspiration. These analyses require high-quality data on hemoglobin and urinary excretion.

Estimating Cl_o is also a way to account for a drift in the hemoglobin baseline, which occurs during fluid therapy performed in the presence of catecholamine treatment.[40]

Analyzing the increase in serum sodium has been used to create a model of the volume kinetics of 7.5% saline in sheep.[41]

The one-volume model can be fitted to the dilution of serum sodium resulting from infusion of sodium-free fluid (such as mannitol). After correction for natriuresis, the size of V so obtained is an approximation of the size of the extracellular fluid space.[25,42]

Capillary leakage of plasma proteins can be studied. As plasma proteins but not hemoglobin escape into the interstitium, the difference in plasma dilution between the two markers indicates the net leak of plasma proteins over time (fig. 4).[17] The leakage is then calculated as a weight (or weight per unit of time) by multiplying the difference in fractional volume expansion by the plasma protein concentration. Mass balance calculations may be used for the same purpose, but they do not allow simulations to be performed.[15]

Presenting the Results

Results can be presented by showing the mean values of the parameter estimates for a group of subjects (table 2) or by making a nomogram[17,35,36,43,44] or a plot[19,23,44] of the fractional plasma volume expansion based on these parameter estimates (fig. 5).

The differential equations given in appendix 2 may also be used to make a number of informative predictions:

1. With the two-volume model, the fractional expansion of V_t can be plotted,[44] which is not possible by other methods (fig. 5A).
2. Calculations help to analyze how infused fluid is distributed at any given time.[17] For this purpose, the rate of

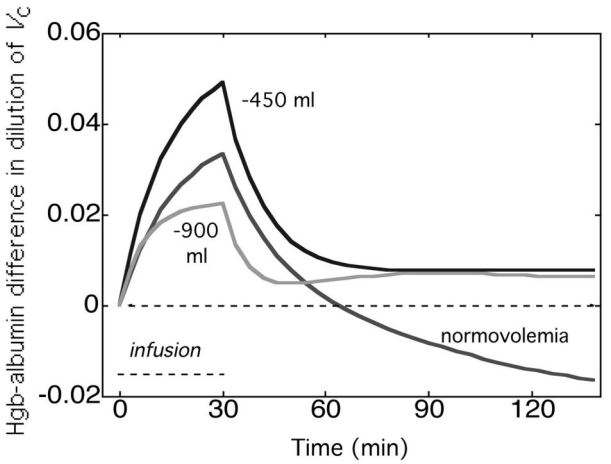

Fig. 4. Endogenous albumin augments plasma volume expansion after hemorrhage despite adequate fluid replacement. Computer simulation based on kinetic data from Ref.[44] in which volunteers received infusions of 25 ml/kg acetated Ringer's solution on three separate occasions. Before two of these infusions, 450 and 900 ml blood was withdrawn. Positive values indicate translocation of albumin from the interstitial fluid to the plasma, whereas negative values show that albumin leaves the plasma. Hgb = hemoglobin.

elimination is given by $Cl\ (v_c - V_c)/V_c$. The volume expansion of V_c and V_t can be generated by multiplying the fractional expansion (*i.e.*, the dilution) of V_c and V_t by their respective baseline volumes[44] (fig. 4). The distribution and elimination can also be highlighted by computer-generated plots (figs. 6 and 7).

3. Simulations may be used to predict the outcome of infusions that have not been performed[22] (fig. 8). This requires that parameter values derived from several infusion volumes and rates have yielded similar plasma dilution-time curves (model linearity).[13,14,32,34]

   Glucose 2.5% solution has been most carefully validated in this respect. In one study, six volunteers received 10 and 15 ml/kg glucose 2.5% solution over 30 min and also 15 and 25 ml/kg over 60 min.[34] The bias (median residual error) associated with simulating plasma dilution in the 24 experiments averaged −0.009 dilution units. Two thirds of this error was due to inability of the glucose kinetics to account for rebound hypoglycemia. The inaccuracy (median absolute residual error) was 0.026 dilution units.

Table 2. Elimination Clearance of Acetated Ringer's Solution under Various Physiologic Circumstances in Adults

	Clearance (ml/min)	References
Healthy volunteers	60–110	3,8,10,11
Pre-eclampsia	125	19
Normal pregnancy	36	19
Thyroid surgery	10	17
Laparoscopic cholecystectomy	7	16
Open abdominal surgery*	21	21

* Patients received lactated Ringer's solution.

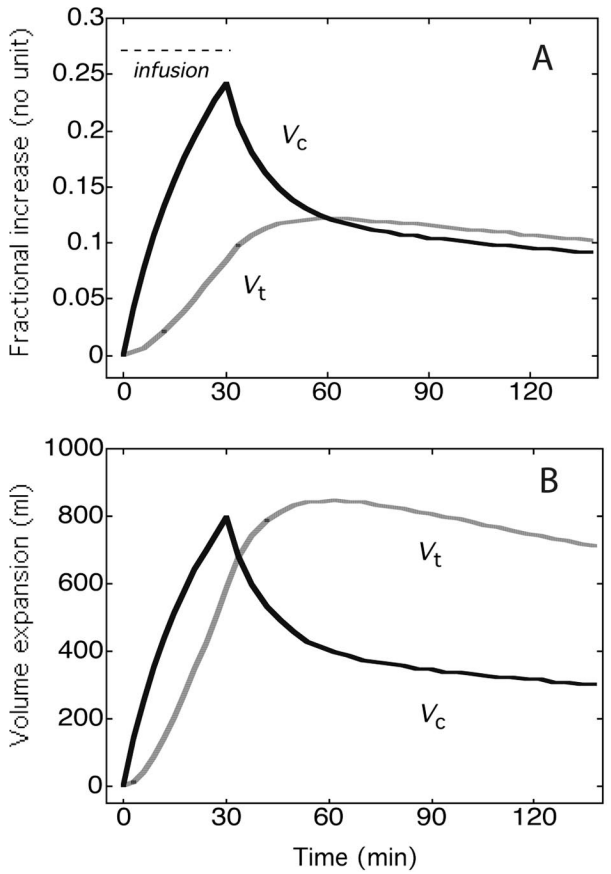

Fig. 5. Computer simulation of the dilution or fractional volume increase (*A*) and the volume expansion (*B*) of V_c (the plasma) and V_t (interstitial fluid) during and after intravenous infusion of 50 ml/min of acetated Ringer's solution during 30 min during thyroid surgery, using kinetic data from Ref.[17]

4. It is used as an aid when designing experiments. For example, it is virtually impossible to have two infusion fluids create the same plasma volume expansion over time without using volume kinetics. Adjusting the infusion rates is an essential challenge when testing whether one of the two fluids exerts an "intrinsic" effect, similar to the case in studies of colloid fluids as well as with artificial blood during shock.

Main Results of Clinical Importance

Distribution Phase

Isotonic or nearly isotonic crystalloid fluids, such as lactated or acetated Ringer's solution, show a distribution phase that requires 25–30 min to be completed.

The effect of distribution is that the plasma volume expansion is, during the actual infusion, larger than the commonly suggested 20–25% of the infused amount. Several studies show that the difference can be substantial. Fifty per-

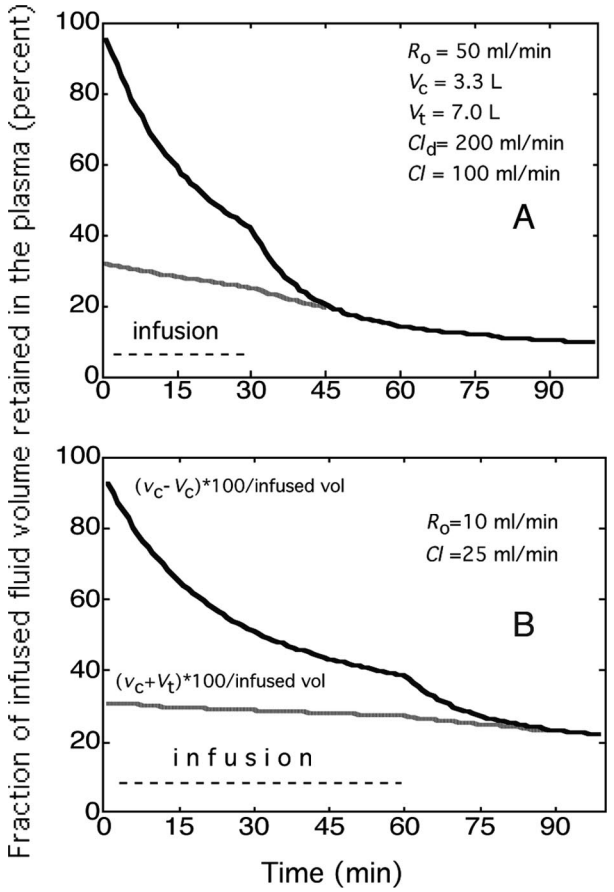

Fig. 6. Computer simulation of the percentage of the amount of infused Ringer's solution that still remains in the plasma, calculated as $(v_c - V_c) \cdot 100$/infused volume, based on typical kinetic data for a brisk 30-min infusion in volunteers (*A*) and a much slower infusion during 60 min in perioperative patients (*B*). The *light lines* show what the fraction would have been if distribution from the plasma to the interstitial fluid space was immediate. Cl = clearance; Cl_d = distribution clearance; R_o = rate of infusion; V_c and V_t = size of central and peripheral fluid spaces, respectively, which are termed v_c and v_t when expanded.

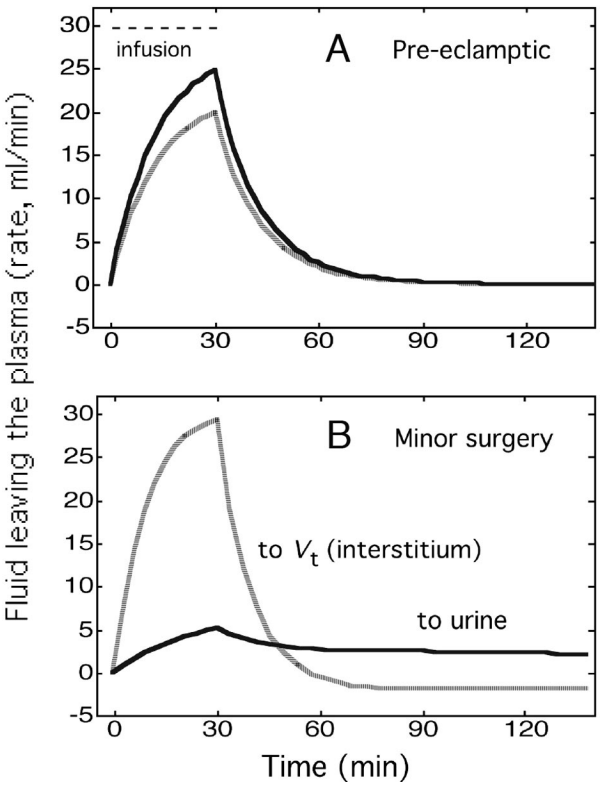

Fig. 7. Computer simulation of how rapidly acetated Ringer's solution leaves the plasma to enter the interstital fluid space (V_t, *light line*) or is excreted as urine (*dark line*). The infusion is given at a rate of 50 ml/min during 30 min. Kinetic data derived from preeclamptic women (*A*, Ref. [19]) and surgical patients (*B*, from the analysis made in fig. 3).

cent of the infused volume resided in the plasma at the end of an infusion of 2 l of acetated Ringer's solution over 30 min in normovolemic volunteers,[44] and this fraction amounted to 65–70% after administration of 1.1 l over 10 min[7] and 2 l over 20 min.[9] Moreover, the retention averaged 60% when acetated Ringer's solution was infused continuously throughout transurethral resection of the prostate performed under general anesthesia.[45]

The fraction of the infused fluid that remains in the plasma is higher for low rates of infusion and decreases with the infusion time.[14] As a rule of thumb, however, the plasma volume expansion at the end of a brisk 30-min infusion is 50–75% larger than would expected if distribution of fluid between V_c and V_t had been immediate.

Figure 6 illustrates the impact of the distribution in volunteers and in surgical patients. The relatively long time required for these fluids to distribute is clinically important as it makes crystalloids better plasma volume expanders than currently acknowledged, at least as long as the infusion is not turned off. Moreover, slow infusions are more effective than bolus infusions.

Low Elimination Clearance during Surgery

The elimination clearance (Cl) for isotonic crystalloid fluid varies greatly depending on whether a patient is conscious or anesthetized. Other factors such as hydration, stress, and trauma also seem to play a role.

Volunteers usually have a Cl of 60–110 ml/min, and the elimination may even be so rapid that the one-volume kinetic model is appropriate.[3,8,10,11] The varying figures for Cl in conscious healthy subjects can probably be explained by differences in body hydration before the fluid challenge. Repetitive infusions are normally followed by a slightly more efficacious elimination.[10,23] In contrast, hemorrhage reduces Cl by 25–50% in a graded manner, even when hypovolemia is quickly restored by crystalloid fluid.[44]

A much lower elimination clearance is found during thyroid,[17] laparoscopic,[16] and open abdominal surgery[21] (table 2). The renal clearance (Cl_r) is then only 5–20 ml/min, which means that only 5–15% of a volume load would be excreted within 2 h during surgery, whereas this fraction is 40–75% in conscious subjects. The half-life for crystalloid

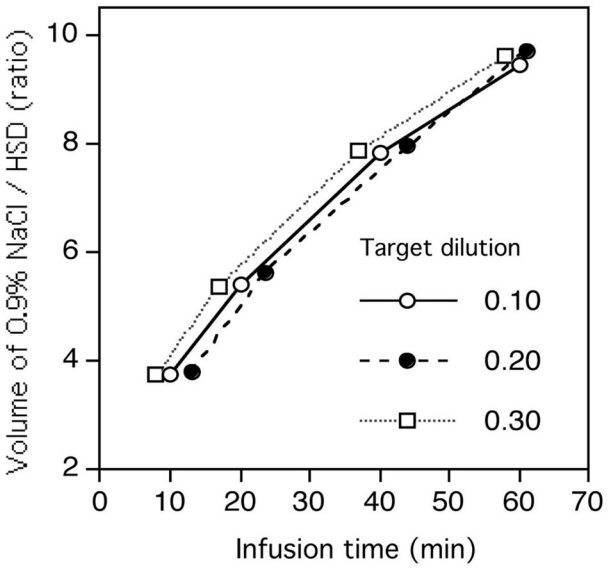

Fig. 8. Comparison of the potency of two infusion fluids. Volume kinetic analysis was first obtained by infusing the fluids (0.9% saline and 7.5% saline in 6% dextran, HSD) in six ewes on separate days. The average parameter values were then used to simulate how much of each fluid was required to dilute the plasma by 10%, 20%, and 30%, when infused at four different rates. The marks show the ratio between the infusion rates needed to reach the target dilution. The potency of HSD relative to 0.9% saline apparently increases with the infusion time and not with the target dilution. Reprinted with permission from Anesth Analg 2002; 95:1547–56.[22]

fluid during surgery (obtained as ln 2·V_c/*Cl*) is even longer than the 2.5 h found for two colloid fluids, 6% dextran 70[3] and albumin 5%,[15] in volunteers. Hormonal changes are probably responsible for much of this reduction. A drift of the baseline for hemoglobin due to vasodilatation might also contribute.

The low *Cl* augments the plasma volume expansion and creates a risk for interstitial edema formation from infusion volumes that otherwise would be no problem for conscious healthy volunteers to excrete. This finding also implies that monitoring of urine flow is ineffective at indicating fluid overload—the urinary excretion simply increases little, despite the presence of a marked surplus of intravascular fluid.[16]

The severe reduction in the elimination clearance is not long lasting. Four hours after laparoscopic cholecystectomy, *Cl* had already assumed the same value as on the day before the surgery.[23] However, patients who had undergone surgery that was preceded by a trauma (hip fracture) had only half as high *Cl* on the first postoperative day as compared with an age- and sex-matched control group.[22]

Role of Stress and Anesthesia in Fluid Retention

Preoperative stress may slightly reduce the clearance of crystalloid fluid. Immediately before the induction of spinal anesthesia, *Cl* averaged 40–60 ml/min,[30] and even lower values have been reported.[29,31] However, a reduced *Cl* before anesthesia might also be due to dehydration caused by preoperative fasting.[23,46]

Induction of anesthesia further reduces *Cl*.[29–31] When isoflurane anesthesia was continued for 3 h in volunteers, there was an overall decrease in *Cl* for 0.9% saline by 50%, although no surgery was conducted.[9] The drop was coupled with a marked increase in the serum renin and aldosterone levels. Hence, anesthesia can explain some but not all the low *Cl* for crystalloid fluid during surgery.

Catecholamines change the disposition of 0.9% saline in sheep. β-Adrenergic stimulation by isoprenaline increases the plasma volume expansion and decreases *Cl*, whereas α-adrenergic stimulation by phenylephrine exerts the opposite effects.[40]

Delayed Distribution during Anesthesia

The distribution clearance (Cl_d) drops by approximately 50% during the onset of spinal, epidural, and general anesthesia,[29–31] which quickly increases the plasma volume expansion resulting from an ongoing infusion.

The mechanism is thought to be lowered intravascular hydrostatic pressure caused by the vasodilatation that accompanies these anesthetics. Therefore, it is of no surprise that the postinduction Cl_d correlates with the associated reduction in the arterial pressure.[30,31] The amount of infused fluid also seems to be of importance. Hence, Cl_d became slightly negative already in the average patient receiving spinal anesthesia preceded by 5 ml/kg as a bolus infusion[20]; this means that flow occurred against the dilution gradient between V_c and V_t. With a volume load of 20 ml/kg given slowly, distribution would be arrested ($Cl_d = 0$) if the mean arterial pressure drops by 60%,[30] whereas only 20% would be required when approximately 15 ml/kg is infused[31] (fig. 9).

Cl_d is only slightly reduced during prolonged surgery,[17] which is probably due to the fact that interstitial oncotic forces eventually counteract further retention of infused fluid in the plasma.[47] Hence, volunteers receiving 0.9% saline had only a 25% lower Cl_d during experimental isoflurane anesthesia lasting for 3 h as compared with the Cl_d measured when they were given the same fluid in the conscious state.[9]

Small Size of V_c during Induction of Anesthesia

In general, *Cl* and Cl_d vary much more than V_c and V_t depending on the physiologic situation. However, a confusing finding is that the calculated V_c becomes 50% smaller if volume kinetics is determined during the onset of spinal,[29,30] epidural,[31] and general anesthesia.[30,31] No satisfactory explanation exists at present, but the small V_c is mathematically due to a marked increase in plasma dilution at that time. If this dilution would be the same throughout the cardiovascular system, the calculated plasma volume expansion would exceed the infused fluid volume. Therefore, a speculation is that, with arterial hypotension, the infused fluids primarily distribute into a smaller volume, such as well-perfused vascular beds with short transit times and the central blood volume; we know that hypotension develops first and the excessive plasma dilution a few minutes later.[48]

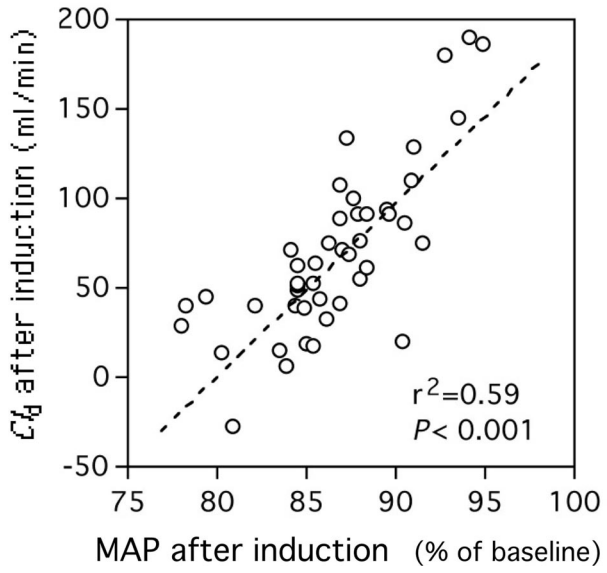

Fig. 9. The mean arterial pressure (MAP) after induction of either general anesthesia with propofol or epidural anesthesia with ropivacaine *versus* the distribution clearance (Cl_d) for lactated Ringer's solution measured after the induction. A lowered MAP retards distribution of the fluid from the plasma to the interstitial fluid space so much as to finally become arrested when $Cl_d = 0$. Based on data from Ref. 31.

Glucose Solutions

Glucose 2.5% and 5% expand the plasma volume just as much as acetated Ringer's solution.[33] However, the expansion after infusion of glucose 5% does not last long because the fluid volume is cleared from the V_c and V_t by both urinary excretion and uptake to the intracellular fluid space along with the administered glucose.[37]

The *Cl* of both glucose and the fluid load was decreased by approximately ⅔ when glucose 2.5% was infused during laparoscopic cholecystectomy.[35] On the first day after hysterectomy, the fluid *Cl* was normal or high (*Cl* = 130 ml/min), whereas the *Cl* for glucose was still on the low side.[36]

In a group of diabetics, the fluid *Cl* for glucose 2.5% was normal (average 99 ml/min) but patients with known impairment of renal function were not studied.[49]

Hypertonic Fluids

Normal saline (0.9%) is 10% more potent as a plasma volume expander than are lactated and acetated Ringer's solution in humans, and this is due to slower elimination.[11] Hypertonic (7.5%) saline is four times more potent, and hypertonic saline in 6% dextran (HSD) is seven times more potent than 0.9% saline.[11] The potency of each fluid was assessed as the volume required to expand the plasma volume by 20% in 30 min.

Hypertonic saline recruits water from the intracellular space quickly.[50] Thereafter, 15 min is required for the infused and recruited volume to distribute throughout the extracellular fluid space.[11,41] *Cl* correlates strongly with the natriuresis.[41]

A distribution phase for HSD occurs in sheep[32] but not in humans.[11] Figure 8 depicts that the difference in potency between HSD and 0.9% saline is strongly dependent on the infusion time.[29] Besides explaining why the potency of HSD is reported differently in various studies, such computer simulations indicate that HSD is not a bad choice for longer infusions, although it is recommended to be administered as a bolus. The increasing difference in potency with time can be understood from the fact that the body does not very easily excrete dextran and a surplus of sodium.

Colloid Fluids

Colloids fluids, such as 6% dextran 70 and 5% albumin, expand a single body fluid space the size of which is similar to the expected plasma volume.[3,15]

During induction of spinal anesthesia before Cesarean section, 3% dextran 70 distributed slowly from V_c to V_t, probably because of the presence of dextran, but Cl_r was similarly small for 3% dextran and acetated Ringer's solution (8–16 ml/min).[29]

Administration of hydroxyethyl starch 130/0.4 during laparoscopic cholecystectomy greatly increased the rate of disappearance of acetated Ringer's solution from the plasma when infused 4 h later.[27] Cl_r also increased, but not as much. This study shows that, when preceded by the colloid fluid, the postoperative infusion of acetated Ringer's solution was of little value for plasma volume expansion as it merely promoted tissue edema and urinary excretion.

Isoflurane and "Nonfunctional" Fluid Spaces

Infusion of 0.9% saline in sheep during isoflurane anesthesia is associated with a marked and systematic discrepancy between model-predicted elimination and the measured urinary excretion, which may be interpreted as allocation of fluid to nonfunctional spaces (the term "third-spacing" has also been used).[51] The aberrant handling of fluid is not caused by mechanical ventilation but by the use of isoflurane *per se*.[52]

This tendency is less pronounced but still significant in anesthetized humans. In patients undergoing thyroid surgery, this allocation to nonfunctional spaces occurred at a rate of 2.0–2.2 ml/min and finally amounted to 20–23% of the infused fluid volume, regardless of whether anesthesia was performed with propofol or with isoflurane.[17] Approximately 25% of this rate can be accounted for by insensible water loss.

Allocation of fluid to nonfunctional spaces means that a fraction of the infused fluid is not available for excretion, at least not within the period of study. From a clinical point of view, the phenomenon probably contributes to the increase in body weight by 25–50% of the crystalloid fluid volume infused perioperatively that lasts throughout the first week after colorectal surgery.[53]

Alternative Kinetic Models

The term "volume kinetics" should be reserved for the mathematical analysis of fluid distribution and elimination based on frequent measurements of plasma dilution and (possibly) also on the urinary excretion. A number of other models for the study of fluid shifts have also been developed. They are usually based on mass balance principles and apply fixed values for several microvascular and physiologic parameters derived from studies of rats, dogs, and humans. A whole-body model by Gyenge *et al.*[54] predicted that 88% of infused 0.9% saline is retained in the plasma at the end of a 6-min bolus,[55] which is consistent with volume kinetic calculations (fig. 6A). Their model can also estimate certain microvascular parameters and the urinary excretion during volume loading[55] and hemorrhage.[56] The urinary excretion is indeed governed by the fractional plasma volume expansion, although the reported *Cl* is higher than that in most volume kinetic studies.[57]

Modeling by Wolf[50] based on data from dogs predicted well the relatively slow distribution of fluid between V_c and V_t during infusion of 0.9% saline.[11] As in volume kinetics, distribution occurs relatively faster after infusion of hypertonic saline,[41] which is due to an vasodilatation-associated increase in capillary filtration capacity.[58]

Mathematical modeling of fluid shifts has rarely been applied to anesthesia and surgery. Using bioimpedance, however, Tatara *et al.*[59] predicted that edema would develop in injured tissues if the operating time is more than 3 h and that there is a risk of interstitial edema if the operating time is more than 6 h.

Conclusions and Future Views

Volume kinetics allows analysis of the kinetics of any infusion fluid. Their disposition in the body can also be predicted and compared by simulation. Volume kinetics has been a research method, used so far only by a small number of investigators, to study crystalloid fluid under various conditions. It is a tool to quantify an effect, which is of value even if the effect *per se* has been known for a long time.

The most challenging findings so far include the increase in plasma volume expansion, from 30% to approximately 50% of the administered fluid volume at end of a 30-min infusion, that is attributable to the time required for distribution of crystalloid fluid from V_c to V_t. This delayed distribution effect is slightly more pronounced during general anesthesia than in the conscious state. However, it is most apparent during the onset of spinal, epidural, and general anesthesia. Then, the distribution of fluid from the plasma to the interstitium might even be arrested. The effect is dependent on the decrease of the arterial pressure and boosts the plasma volume expansion in response to infused fluid.

The elimination of crystalloid fluid undergoes two modifications in association with anesthesia and surgery. The first one consists in a powerful but temporary reduction of Cl_r, which then becomes similar to the *Cl* of a colloid fluid. The urinary excretion then increases little even in the presence of marked plasma volume expansion. This remarkable lowering of Cl_r makes it inappropriate to extrapolate findings made with crystalloid fluids in volunteers to the operating room.

The second modification also promotes the development of edema but, in contrast to the change in Cl_r, not to an increased plasma volume expansion. The second modification results in a fraction of the infused crystalloid fluid becoming unavailable for excretion, perhaps by accumulating outside the two functional spaces V_c and V_t rather than allowing for the free exchange of fluid between them. Such allocation to a third but nonfunctional space might give rise to longstanding edema. Attempting to normalize the situation by drugs acting on adrenergic receptors is a current line of research. In such work, quantification of the allocation of fluid to nonfunctional fluid spaces by volume kinetic analysis is an essential tool.

One problem that prevents clinical use of volume kinetics is that a complete analysis in a volunteer or patient requires a series of as many as 25–40 precise hemoglobin measurements. On the other hand, the cumbersome procedure would be simplified if the traditional invasive measurements could be replaced by noninvasive hemoglobin monitoring.

Another problem is that an outcome study after placing patients on variable degrees of steady-state plasma dilution during surgery is lacking. Such a study is of general interest, but also opens a possibility for the anesthesiologist to perform intraoperative fluid management based on a feedback loop using the combination of a noninvasive hemoglobin monitor, volume kinetic model, and a fluid pump.

Appendix 1

Hemoglobin-derived Plasma Dilution

The hemoglobin-derived plasma dilution is used to indicate the dilution of the plasma in the central body fluid space expanded by the infused fluid, $(v_c(t) - V_c)/V_c$. The reference equation for this relationship is

$$\frac{v_c(t) - V_c}{V_c} = \frac{\frac{Hgb - Hgb(t)}{Hgb(t)}}{1 - Hct} = \frac{\frac{Hgb}{Hgb(t)} - 1}{1 - Hct},$$

where v_c is the size of the expanded central body plasma fluid space, V_c is the same body fluid space at baseline, Hct is the hematocrit, and Hgb is the hemoglobin concentration in whole blood at baseline or at time (t). Symbols without an index denote baseline values and (t) those obtained at a later point in time.

The erythrocyte count is ideally measured on the same samples as the hemoglobin concentration. This is obtained by another method (light dispersion of a laser beam) than hemoglobin (photometry) but is diluted in the same way during volume loading. Therefore, to make the calculated dilution less sensitive to technical errors, it is advisable that the average dilution of hemoglobin and the erythrocyte count is used in the curve-fitting procedure. Moreover, a correction for changes in mean corpuscular volume should be made in case the infusion modifies the plasma osmolality (see appendix 3).

Plasma dilution calculated from plasma proteins should not involve the factor (1 − hematocrit) because these concentrations are measured on the plasma fraction of the blood.

Appendix 2

The Two-volume Model

The volume change of v_c is given by the rate of infusion (R_o) minus the baseline fluid losses (Cl_o), the elimination (Cl · plasma dilution) and the distribution of fluid to v_t in which the rate is governed by a clearance, Cl_d (fig. 2). The differential equation is

$$\frac{dv_c}{dt} = R_o - Cl_o - Cl\frac{(v_c(t) - V_c)}{V_c} - Cl_d\left[\frac{(v_c(t) - V_c)}{V_c} - \frac{(v_t(t) - V_t)}{V_t}\right]$$

Volume changes of v_t are determined only by the balance in dilution between V_c and V_t and the rate of equilibration is governed by Cl_d. The differential equation is

$$\frac{dv_t}{dt} = Cl_d\left[\frac{(v_c(t) - V_c)}{V_c} - \frac{(v_t(t) - V_t)}{V_t}\right]$$

Hence, v_t increases faster if Cl_d is high and also decreases more promptly when fluid is eliminated from v_c by the mechanisms Cl_o and Cl. As fluid does not bind to tissue, Cl_d is given the same value for translocation of fluid in both directions. There is evidence that the interstitial fluid compliance cannot be greatly modified by a modest volume load,[10] but the finding that a computer estimate of Cl_o is often higher than the known insensible water loss increases the suspicion that Cl_d is lower when fluid is returned from v_t to v_c as compared with when fluid is translocated from v_c to v_t.[17] Alternatively, fluid accumulates in a third "nonfunctional" space.

Problems in separating V_t and Cl may become apparent if the experiment is short or the elimination is slow. If we assume that nearly all elimination occurs by virtue of renal excretion and no accumulation of fluid in nonfunctional spaces ("third-spacing") occurs, Cl may be set equal to the renal clearance (Cl_r) of the infused fluid[8]:

$$Cl_r = \frac{\sum urine\ volume}{AUC\ for\ \frac{(v_c(t) - V_c)}{V_c}}$$

The One-volume Model

The volume change of the single body fluid space V is governed by the rate of infusion (R_o) minus the baseline fluid losses (Cl_o) and the elimination (Cl · plasma dilution). The differential equation is

$$\frac{dv}{dt} = R_o - Cl_o - Cl\frac{v(t) - V}{V}$$

A much higher model-predicted Cl than the value of Cl_r determined by the urinary excretion strongly suggests the existence of a peripheral fluid compartment (V_t). Discrimination between the two models can also be made by statistics, based on the squared differences between best model-predicted and measured data points.[2–4,7–10]

Least-squares Regression

Curve fitting using a least-squares regression routine is normally based on the solutions to the differential equations shown above. Both numerical[2] and matrix[3,8,11] solutions have been published. Some mathematical software is able to estimate the model parameters using only the crude differential equations.

The F Test

An F test might be applied to help decide whether the one- or two-volume model should be applied.[2–4] This test holds that the use of a more complex model must markedly reduce the squared deviations between computer-generated and measured data points or else the simpler model should be preferred. An F value is obtained as follows:

$$F = \frac{MSQ_{1\text{-}vol} - MSQ_{2\text{-}vol}}{MSQ_{1\text{-}vol}} \cdot \frac{df_{2\text{-}vol}}{df_{1\text{-}vol} - df_{2\text{-}vol}},$$

where MSQ is the mean square error for the difference between the measured dilution of the plasma volume and the optimal curve-fit according to the one-volume (1-vol) and two-volume (2-vol) model, respectively. Df is the degrees of freedom, *i.e.*, the number of data points used in fitting the function minus the number of parameters fitted. The calculated value for F is compared with the critical value for significance in a standard statistical F table.

Appendix 3

Correction for Blood Loss and Sampled Volume

The reference equation for hemoglobin-derived plasma dilution can be applied directly in the curve-fitting procedure if losses of hemoglobin by blood sampling and hemorrhage are negligible. As long as a series of blood samples are usually secured, however, these losses of tracer should normally be considered in the calculations. They create a "false" dilution that is not a result of the fluid therapy. The correction of the "false" dilution requires the assumption of a blood volume (BV) at baseline, which is usually based on the height and weight of the subjects.[2–4,10,11] The total hemoglobin mass (MHgb) is first obtained and the expanded blood volume at a later time is then obtained (BV(t))[60]:

$$MHgb = BV \cdot Hgb$$

$$MHgb(t) = MHb - [(sampled + bled)\ volume \cdot Hgb\ (t)]$$

$$BV(t) = \frac{MHgb(t)}{Hgb(t)}$$

This expression is converted from blood volume to plasma volume (PV) data. Finally, changes in erythrocyte size are considered by adding a term for the relationship between the mean corpuscular volume at baseline (MCV) and at the later time (MCV[t]):

$$PV = BV \cdot (1 - Hct)$$

$$PV(t) = BV(t) \cdot \left[1 - Hct \cdot \frac{Hgb(t)}{Hgb} \cdot \frac{MCV(t)}{MCV}\right]$$

$$\frac{v_c(t) - V_c}{V_c} = \frac{PV(t) - PV}{PV}$$

Here, the mean value for the hemoglobin and erythrocyte dilution is used as the "Hgb-derived plasma dilution." Note that the relationship between the baseline Hgb and a diluted value obtained later is written as Hgb/Hgb(t) in the reference equation, whereas the inverse relationship is used when the hematocrit is corrected for dilution.

Plasma dilution based on the concentrations of plasma proteins require slightly different calculations.[17]

Simulations show that the error introduced by assuming too low or too high an initial blood volume is small.[44] The error associated with applying an erroneous blood sampling volume is larger because blood sampling is done frequently in volume kinetic studies.

Appendix 4

Osmotic Fluid Shift

When infusing hypertonic fluid, an osmotic shift occurs across the cell membrane and exchanges water from the intracellular (40% of the body weight) to the extracellular fluid space (20% of the body weight).[61] Using the baseline serum osmolality, which is approximately 295 mosmol/kg, the translocated volume f_t can be obtained from[11,32]:

$$\frac{BW \cdot 20\% \cdot 295 + \textit{infused osmoles}}{BW \cdot 20\% + f_t + \textit{infused volume}} = \frac{BW \cdot 40\% \cdot 295}{BW \cdot 40\% - f_t}$$

where BW = body weight. Applying the calculated osmolality of 2458 for 7.5% NaCl, this equation indicates that the first infused milliliter translocates 4.9 ml of water in an adult weighing 70 kg. The osmotic force then becomes progressively reduced for each subsequent amount of infused fluid, and it is recommended that f_t be entered as a linear function in the analysis process in which f_t at each point in time is governed by the total amount of infused fluid.

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