Volume Kinetics of Ringer's Solution in Hypovolemic Volunteers

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Background: The amount of Ringer's solution needed to restore normal blood volumes is thought to be three to five times the volume of blood lost. This therapy can be optimized by using a kinetic model that takes accounts for the rates of distribution and elimination of the infused fluid.

Methods: The authors infused 25 ml/kg Ringer's acetate solution into 10 male volunteers who were 23 to 33 yr old (mean, 28 yr) when they were normovolemic and after 450 ml and 900 ml blood had been withdrawn. One-volume and two-volume kinetic models were fitted to the dilution of the total venous hemoglobin and plasma albumin concentrations.

Results: Withdrawal of blood resulted in a progressive upward shift of the dilution-time curves of both markers. The two-volume model was statistically justified in 56 of the 60 analyzed data sets. The hemoglobin changes indicated that the body fluid space expanded by the infused fluid had a mean total volume of 10.7 l (±0.9 SEM). The elimination rate constant (k) decreased with the degree of hypovolemia and was 133 ml/min (22 ml/min [SEM], 100 ml/min (39 ml/min [SEM]), and 34 ml/min (7 ml/min [SEM]), respectively (P < 0.01). Plasma albumin indicated a slightly larger body fluid space expanded by the infused fluid, but k was less (P < 0.02). Hypovolemia reduced the systolic and diastolic blood pressures by approximately 10 mmHg (P < 0.05).

Conclusions: The dilution of the blood and the retention of infused Ringer's solution in the body increases in the presence of hypovolemia, which can be attributed chiefly to a reduction of the elimination rate constant. (Key words: Fluid therapy; hemodilution; pharmacokinetics; saline solution; serum albumin.)

INTRAVENOUS administration of crystalloid fluids, such as Ringer's solution buffered with lactate or acetate, is used commonly to treat hypovolemia. However, certain questions associated with the use of Ringer's solution in hypovolemic persons are still unclear. Because the infused fluid is believed to be distributed throughout the extracellular fluid volume, it is usually infused in an amount equal to three to five times the estimated blood deficit.1,2 Labeling the infused fluid with a tracer substance, however, indicates the existence of both expandable and nonexpandable regions within the body, and the volume of an infused fluid can be located only in a body fluid space that is expandable.3,4 In addition, the volume effect of Ringer's solution has a time course that determines the optimal rate of infusion for the fluid. The blood volume is expanded most during and just after the infusion, but the expansion becomes less pronounced with time.

To overcome these problems, we have worked with a kinetic model that allows a nonstationary description of the fluid status. The distribution and elimination of Ringer's acetate solution were analyzed in male volunteers subjected to acute hypovolemia by withdrawing 450 ml and 900 ml, respectively, of venous blood. The disposition of infused fluid was evaluated by fitting one-volume and two-volume models to the dilution of the blood hemoglobin (h-Hb) and serum albumin concentrations.3-7 The optimal rates of infusion required to restore and maintain normal blood volume were then calculated using a computerized simulation procedure based on the obtained values of the kinetic parameters.3

Materials and Methods

Ten healthy men between the ages of 23 and 33 yr (mean, 28 yr) and who weighed 65 to 85 kg (mean, 76 kg) participated in the study. Our local ethics committee approved the protocol, and all the volunteers gave informed consent.

Procedure

All the volunteers underwent three intravenous infusion experiments with 25 ml/kg Ringer's acetate solution (Pharmacia, Uppsala, Sweden) given at a constant rate during a period of 30 min via an infusion pump...
(Flo-Gard 6201; Baxter Healthcare Ltd., Deerfield, IL). The ionic content of this fluid was 130 mEq/l Na, 4 mEq/l K, 2 mEq/l Ca, 1 mEq/l Mg, 30 mEq/l acetate, and 110 mEq/l Cl. The experiments were performed in random order and on separate days at least 1 week apart. After an overnight fast, the volunteers rested comfortably on a bed for at least 20 min before the experiments started at 8.30 a.m. They consisted of (1) an intravenous infusion of Ringer’s solution without blood withdrawal (normovolemia, one occasion), (2) an intravenous infusion of Ringer’s solution after withdrawal of 450 ml venous blood (mild hypovolemia, one occasion), and (3) an intravenous infusion of Ringer’s solution after withdrawal of 900 ml blood (moderate hypovolemia, one occasion). The blood was removed from the circulation during a period of approximately 10 min and 15 min, respectively, using a blood donor set (Teruflex; Terumo Corp., Tokyo, Japan). The crystalloid infusion was started as soon as baseline measurements for the study had been performed, approximately 2 min after the end of the blood withdrawal. Collected blood was returned to the volunteer after each experiment was completed. Nausea or vertigo in association with blood withdrawal was treated with 5 mg ephedrine administered intravenously, which was repeated if necessary.

Measurements
Before any fluid was administered, a cubital vein of each arm was cannulated for the purpose of withdrawing and sampling blood and for infusing fluid. In all groups, venous blood (8 ml) was collected every 5 min for 60 min and thereafter every 10 min for as long as 180 min after the infusion started. A tourniquet was not used. After a blood sample was drawn, 3 ml Ringer’s solution was injected to flush the cannula, and a 2-ml sample to be discarded was drawn before each blood sampling to avoid undue hemodilution caused by this fluid. Before blood withdrawal and before each infusion of crystalloid, one sample was drawn in duplicate and the mean value was used in the calculations. The mean of the latter of these duplicate samples was used as a “baseline.” but both pairs were used to calculate the coefficient of variation for the analyses performed.

The BHb concentration was measured using a Technicon H-2 (Bayer, Tarrytown, NY) using colorimetric analysis at 546 nm. The serum albumin concentration was measured using bromcresol green, followed by reflection spectrophotometry (Ektachem 250/950 IRC, Johnson & Johnson, Rochester, MN). The coefficient of variation was 1% for BHb and 2.6% for serum albumin.

The volunteers voided just before the experiments were started and (while the recumbent position) whenever they reported urgency.

Bioelectric impedance analysis using a Xitron 4000B Spectrum Analyzer (Xitron Technologies, San Diego, CA) to estimate the total body water and extracellular water volumes was performed before blood withdrawal, immediately after blood withdrawal, and just after the infusion of Ringer’s acetate solution was complete. Each reported bioimpedance value is the mean of three successive recordings. The same body weight was used as an input variable in all estimations of these anatomic body fluid spaces, which were performed by the software delivered together with the apparatus.

Kinetic Models
The distribution of the fluid given by intravenous infusion was analyzed using volume-of-fluid-spaces kinetic models, which can be summarized as follows: a fluid given by intravenous infusion at a rate \( k_v \) is distributed in an expandable space with a volume \( V \), which the system strives to maintain at an ideal (target) volume \( V_t \). Fluid leaves the space at a basal rate, representing perspiration and baseline diuresis \( k_m \) (fixed rate), and at a rate proportional by a constant \( k_v \) to the deviation from the target volume \( V_t \) (fig. 1, top). The rate of fluid elimination from the system at any time in this single-fluid space model is then given by the product of \( k_v \) (unit, ml/min) and the dilution of \( V_t \) that is, \( (V_t - V)/V \) (no unit) in addition to the elimination given by \( k_m \) (ml/min), which is of zero order and not directly related to the other parameters in the model.

In the two-volume space model (fig. 1, bottom), the central fluid space communicates with a peripheral fluid space. The net rate of fluid exchange between the expandable fluid spaces (with volumes \( V_1 \) and \( V_2 \)) is proportional to the relative difference in deviation from the target values \( V_1 \) and \( V_2 \) by a constant \( k_2 \). The system strives to maintain the target volumes by acting on the controlled elimination mechanism in proportion, \( k_2 \), to the relative deviation from the target volume of the central fluid space \( V_1 \). Thus, the rate of elimination of fluid from the system, in addition to the baseline rate \( k_m \), is given by the product of \( k_v \) and the dilution of \( V_1 \) that is, \( (V_1 - V)/V_1 \).

The differential equations describing the assumptions of the one-volume and two-volume fluid space models have been described in recent publications. Analytic and numeric solutions to these differential equations have also been given.
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![Diagram](https://example.com/diagram.png)

Fig. 1. The one-volume kinetic model (top) and the two-volume kinetic model (bottom) used to calculate the size of the body fluid space expanded by an intravenous infusion of Ringer’s solution.

Data Analysis
The dilution of the plasma as indicated in venous blood was assumed to reflect an increase in the volume of one or more expandable body fluid spaces. The plasma was chosen because the extracellular fluid (but not the erythrocytes) is expanded by infused Ringer’s solution. For this purpose, the data on serum albumin were used directly. The baseline hematocrit obtained just before the crystalloid infusion started was corrected to allow the calculation of the dilution of the plasma from the fractional change in B-Hb concentration. Because the sampled plasma is a part of V (or V₁), the dilution at time t is obtained as:

\[
\frac{(v(t) - V)}{V} = \frac{\text{[baseline B-Hb/B-Hb}(t) - 1]}{(1 - \text{baseline hematocrit})}
\]

We did not account for the fact that the hematocrit in the capillaries, which occupies approximately 5% of the blood volume, is less than in the large blood vessels, but the calculations were corrected for the losses of erythrocytes and albumin with the withdrawal of blood and the sampling volume. This correction of the calculated dilution of the plasma was made by subtracting all losses of hemoglobin and albumin from the estimated total amounts of hemoglobin and albumin in the blood, which are the products of the baseline blood and plasma volumes and baseline B-Hb and serum albumin concentrations. The baseline blood volume was estimated according to the following equation:\(^{11}\):

Blood volume (liters) = 0.03219 weight (kg)

\[+ 0.3669 \text{ length}^3 (m) + 0.6041\]

The baseline plasma volume was obtained by multiplying the baseline blood volume by (1 – baseline hematocrit). The corrected dilution-time profiles were used as an input variable in the calculations.

A kᵢ of 0.8 ml/min (≈1,150 ml/24 h) was used before in healthy volunteers who had fasted overnight\(^{4}\) and corresponds to an insensible fluid loss of 10 ml/kg per day\(^{12}\) with an addition for a fluid loss with the blood sampling of 0.5 ml/min. The baseline net fluid losses from the expandable fluid space are expected to be reduced in the presence of hypovolemia. This results from the inhibition of spontaneous diuresis and also from a shift of fluid from the cells to the extracellular space caused by increased osmolality, which restores the volume of blood lost within approximately 24 h.\(^{13-15}\) To account for this compensation, kᵢ was set to 0.4 ml/min when 450 ml blood was withdrawn, and to 0 ml/min when 900 ml blood had been withdrawn. The lesser values also yielded a smaller sum of squared errors than a kᵢ of 0.8 ml/min when the kinetic models were fitted to the data.

The model parameters were calculated on a computer using Matlab version 4.2 (MathWorks, Natick, MA) in which a nonlinear least-squares regression routine based on a modified Gauss-Newton method was repeated until no parameter changed by more than 0.001 (0.1%) in each iteration. Curve fitting was performed on the one-volume fluid-space model for which the output consists of the best estimates and standard errors for V and kᵢ. Calculations were also done according to the two-volume fluid space model in which the output consists of the best estimates and standard errors for V₁, V₂, kᵢ, and kᵢ. Repeated analysis using a fixed kᵢ, determined by the urinary excretion was performed in experiments in which the two-volume model was statistically justified but the correlation matrix showed strong within-patient covariances (r ≤ −0.98) between kᵢ and V₂. In these cases, the conventional way of applying the two-volume model makes it difficult to distinguish between fluid

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distribution and elimination. Because the urinary excretion correlates well with the model-predicted elimination of fluid, this approach can be used to make the two-volume model more stable. To calculate the fixed $k_r$, the total volume of excreted urine was divided by the integral of the dilution-time curve for the corresponding period of time, assuming that one half of the spontaneous elimination of fluid ($k_b$) appeared as urine.

**Simulations**

Simulations were performed using the Matlab computer program to identify different combinations of infusion rates and infusion times that would yield a predetermined dilution of $V_1$. The mean values of the parameter estimates in the two-volume fluid-space model were used to identify the fluid regimen resulting in dilutions of 2%, 5%, 10%, 15%, 20%, 25%, and 30%. We also performed simulations to identify the infusion rate that yielded steady-state dilution 30 min after the target dilution had been obtained.

**Statistics**

The results are reported as the mean and the standard error of the mean (SEM). The statistical evaluation was performed using one-way analysis of variance, repeated-measures analysis of variance followed by Dunnett's test, and the paired $t$-test. The results of the two-volume model were reported if the following $F$ test showed that the sum of squared errors was significantly reduced when a biexponential curve rather than a monoeponential curve was fitted to the data:

$$F = \left[ \frac{SSQ_{VOF51} - SSQ_{VOF52}}{SSQ_{VOF52}} \right] \times \left[ \frac{df_{VOF52}}{df_{VOF51} - df_{VOF52}} \right]$$

where SSQ is the sum of squared errors for the difference between the dilution of the plasma and the optimal curve fit according to the one-volume model (VOFS1) and the two-volume model (VOFS2), respectively. $df$ represents 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 table. $P < 0.05$ was considered significant.

**Results**

The dilution of the B-Hb and plasma albumin concentrations increased during the infusion and decreased rapidly during the first 30 min after the infusion, but subsequent reductions of the dilution usually occurred more slowly. Withdrawal of blood resulted in a progressively upward shift of the dilution-time curves of both markers (fig. 2).

**Kinetic Analysis**

Fitting the kinetic models to the dilution data showed that the two-volume model was usually statistically justified, with the only exceptions being a few analyses based on B-Hb (tables 1 and 2). Repeated-measures analysis of variance based on the results obtained from the two-volume model showed that $k_r$ decreased with the amount of withdrawn blood (B-Hb, $P < 0.01$; serum albumin, $P < 0.04$). For both markers, moderate hypovolemia was associated with a significantly less $k_r$ than normovolemia (by Dunnett's test). The other parameters did not differ between the groups (figs. 3 and 4).

The volume of the central fluid space ($V_c$) was larger when the analysis was based on the serum albumin concentration ($P < 0.01$), but the values of $V_2$, $k_r$, and $k_b$ did not differ significantly depending on the marker used to indicate the dilution of $V_1$. The sum of the squared errors was also less when serum albumin was chosen for the curve-fitting procedure ($P < 0.03$).

The statistically justified model (one- or two-volume model) was used in each experiment for further comparisons between the kinetic parameters. When all 60 optimal analyses were studied, $k_r$ decreased with the amount of withdrawn blood ($P < 0.01$, by two-way analysis of variance). For the series based on the B-Hb level, $k_r$ was 133 (22 ml/min [SEM]), 100 (39 ml/min [SEM]), and 34 ml/min (7 ml/min [SEM]) for the three series of experiments. There were also differences depending on the marker to indicate the dilution, because the total expandable volume was larger ($P < 0.01$) and $k_r$ was less ($P < 0.02$) when serum albumin was used.

The nomograms shown in figure 5 outline alternative fluid regimens for replacing blood lost with crystalloid fluid. They were created by computer simulation using the two-volume model kinetic parameters obtained when the B-Hb data were analyzed (table 1).

**Autotransfusion, Hemodynamics, and Bioimpedance**

The B-Hb concentration decreased from 13.78 g/100 ml (0.20 g/100 ml [SEM]) to 13.49 g/100 ml (0.22 g/100 ml [SEM]) ($P < 0.01$) during withdrawal of 450 ml blood, and from 13.66 g/100 ml (0.22 g/100 ml [SEM]) to 13.19 g/100 ml (0.19 g/100 ml [SEM]) ($P < 0.001$) when 900 ml
blood was withdrawn. The spontaneous relative decrease of the serum albumin concentration during blood withdrawal was slightly smaller than indicated by these figures.

There was no hemodynamic change when mild hypovolemia was induced, but the systolic pressure decreased from 116 mmHg (3 mmHg [SEM]) to a minimum of 104 mmHg (3 mmHg [SEM]) when the larger amount of blood was withdrawn ($P < 0.01$). Two of these volunteers reported nausea and were given ephedrine intravenously. These were the only experiments in which a drug was given.

The mean systolic and diastolic blood pressures during and after the infusions were significantly less during mild and moderate hypovolemia than during the control experiments (table 3). The volunteers’ heart rates were less during mild hypovolemia and greater during moderate hypovolemia than during normovolemia ($P < 0.05$).

The bioimpedance analyses indicated that the fluid balance status of the volunteers was similar on all three occasions when the experiments were performed (table 3). No change occurred during blood withdrawal, but the infusion of crystalloid fluid increased the volume of the extracellular fluid space compartment from 20.5 l (0.3 l [SEM]) to 21.1 l (0.3 l [SEM]) ($P < 0.0001$). The volume of the total body water did not change significantly.

The sizes of the total expandable volume, as indicated by the dilution of B-Hb and serum albumin concentrations, were 51% (5% [SEM]) and 68% (6% [SEM]) of the extracellular fluid space as measured by bioimpedance. The corresponding fraction of the body weight that was expanded by crystalloid fluid was 14.5% (1.4% [SEM]) and 18.7% (1.7% [SEM]), respectively.

The measured urine excretion tended to decrease with the bleeding: 862 ml (71 ml [SEM]) in normovolemia, 805 ml (127 ml [SEM]) for mild hypovolemia, and 680 ml (150 ml [SEM]) for moderate hypovolemia. These values did not differ significantly between the groups, but all of them do not represent the entire 3-h study period because volunteers could prefer to void at an earlier stage.

**Discussion**

Treatment of acute hypovolemia with crystalloid fluid is an important task for anesthesiologists and other personnel working in trauma care. The current approach to determine the amount of Ringer’s acetate solution needed to treat hypovolemia is based on a kinetic model that accounts for the distribution and elimination of fluid. Graded hypovolemia was induced in awake healthy male volunteers, and the dilution of the plasma over time was analyzed according to the kinetic model.
Table 1. Volume Kinetic Data on an IV Infusion of 25 ml/kg of Ringer Solution Over 30 min in 10 Male Volunteers as Obtained by Analysis of the Plasma Dilution Indicated by the Blood Hemoglobin Concentration

<table>
<thead>
<tr>
<th>Amount of Blood Withdrawn</th>
<th>0 ml</th>
<th>450 ml</th>
<th>900 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>n, total</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>2-volume spaces</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>8</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>V₁ (ml)</td>
<td>3,743 (521)</td>
<td>3,371 (379)</td>
<td>3,039 (407)</td>
</tr>
<tr>
<td>V₂ (ml)</td>
<td>7,623 (1,675)</td>
<td>9,258 (1,501)</td>
<td>7,950 (1,326)</td>
</tr>
<tr>
<td>k₁ (ml/min)</td>
<td>195 (61)</td>
<td>214 (32)</td>
<td>192 (22)</td>
</tr>
<tr>
<td>k₂ (ml/min)</td>
<td>63 (20)</td>
<td>61 (19)</td>
<td>39 (12)</td>
</tr>
<tr>
<td>k₃ (ml/min)</td>
<td>107 (16)</td>
<td>44 (7)</td>
<td>34 (7)</td>
</tr>
<tr>
<td>Fixed k₄ (n)</td>
<td>28 (7*)</td>
<td>19 (8*)</td>
<td>6 (2)*</td>
</tr>
<tr>
<td>SSQ (10⁻¹²)</td>
<td>6.7 (0.7)</td>
<td>11.7 (2.2)</td>
<td>9.2 (1.7)</td>
</tr>
<tr>
<td>1-volume space</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>V (ml)</td>
<td>4,290 (68)</td>
<td>6,097 (2,127)</td>
<td></td>
</tr>
<tr>
<td>k₁ (ml/min)</td>
<td>482 (124)</td>
<td>700 (398)</td>
<td></td>
</tr>
<tr>
<td>k₂ (ml/min)</td>
<td>239 (28)</td>
<td>321 (66)</td>
<td></td>
</tr>
<tr>
<td>k₃ (ml/min)</td>
<td>18 (6)</td>
<td>25 (9)</td>
<td></td>
</tr>
<tr>
<td>SSQ (10⁻¹²)</td>
<td>16.2 (6.2)</td>
<td>9.1 (3.4)</td>
<td></td>
</tr>
</tbody>
</table>

The result is reported according to either the two-volume or one-volume model depending on which one that is statistically justified. The first line for each parameter gives the mean (SEM) of all estimates in the group. The second line shows the precision of these estimates, specified as the mean (SEM) of the standard errors associated with them.

SSQ = sum of squared errors.

* Analyses based on a fixed k₄ are not included.

The results show that the dilution of plasma sampled from the cubital vein during infusion of Ringer's acetate solution increased progressively with larger amounts of withdrawn blood. Further understanding of why the dilution increased can be obtained from the subsequent kinetic analysis. This shows that the elimination rate constant (k₄) was less when blood had been withdrawn; that is, less fluid was eliminated from the system for any specified degree of dilution. In contrast, there was no systematic change in the volume of the total body fluid space expanded by the infused fluid.

The models for analysis of the distribution and elimination of the infused fluid that we used differ in several ways from conventional pharmacokinetic models. The volume kinetic models reflect the expandability of a functional body fluid space, V₁, of which the sampled plasma is a part, and of another more remote peripheral body fluid space, V₂. The rate of elimination is governed by a rate constant kₑ, which has the unit milliliters per minute, and this might suggest that kₑ is a clearance constant. However, this is not appropriate because the volumes of distribution (V₁ and V₂) change constantly during an experiment. Rather, kₑ has the unit milliliters per minute because it is multiplied by the dilution of V₁, which has no unit, to yield the rate of elimination, which is given in milliliters per minute. The rate of volume equilibration between V₁ and V₂ is governed by a constant designated kᵥ₁, which also has the unit milliliters per minute. In addition to estimating the appropriate parameters, the volume kinetic models can be used to simulate the outcome of any infusion rate or sequence of infusion rates. An interesting possibility is that a simulated dilution-time plot (V₁(t) - V₁)/V₁ can be converted into a volume-time plot by multiplying the function by V₁ to obtain V₂(t) - V₁, as shown in fig. 3 and 4.

The anatomic compartment corresponding to V₁ is probably the plasma volume, whereas V₂ is likely to represent expandable parts of the interstitial fluid space (excluding bone tissue and the central nervous system). Analyses based on individual data sometimes fail to identify V₂, however, and then we say that the person studied handles the fluid according to the one-volume model. This is often the case when kₑ is relatively great, which means that the infused fluid is excreted rapidly. The size of the expanded body fluid space then is rarely more than twice the estimated plasma volume. Thus, the fluid is excreted by the kidneys sooner than it fills up.

Table 2. Same Parameters as in Table 1, but Based On Analysis of the Serum Albumin Concentration

<table>
<thead>
<tr>
<th>Amount of Blood Withdrawn</th>
<th>0 ml</th>
<th>450 ml</th>
<th>900 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-volume spaces</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>V₁ (ml)</td>
<td>4,046 (346)</td>
<td>4,030 (487)</td>
<td>3,563 (374)</td>
</tr>
<tr>
<td>V₂ (ml)</td>
<td>11,412 (2,854)</td>
<td>10,851 (1,380)</td>
<td>8,203 (916)</td>
</tr>
<tr>
<td>k₁ (ml/min)</td>
<td>538 (87)</td>
<td>595 (83)</td>
<td>414 (41)</td>
</tr>
<tr>
<td>k₂ (ml/min)</td>
<td>2,638 (905)</td>
<td>2,383 (381)</td>
<td>1,486 (369)</td>
</tr>
<tr>
<td>Fixed k₃ (n)</td>
<td>280 (50)</td>
<td>228 (39)</td>
<td>191 (15)</td>
</tr>
<tr>
<td>SSQ (10⁻¹²)</td>
<td>53 (18)</td>
<td>43 (8)</td>
<td>30 (3)</td>
</tr>
<tr>
<td>1-volume space</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>V (ml)</td>
<td>4,44 (0.8)</td>
<td>6.6 (0.7)</td>
<td>8.7 (2.9)</td>
</tr>
</tbody>
</table>

The result is reported according to the two-volume model which was statistically justified in all analyses. The first line for each parameter gives the mean (SEM) of all estimates in the group. The second line shows the precision of these estimates, specified as the mean (SEM) of the standard errors associated with them.

SSQ = sum of squared errors.

* Analyses based on fixed k₄ are not included.
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![Graphs showing dilution curves for central and peripheral fluid spaces.]

Fig. 3. Superposed model-predicted dilution curves for the central (left) and peripheral (right) fluid spaces when male volunteers given Ringer’s solution by intravenous infusion were normovolemic and when 450 ml and 900 ml blood had been withdrawn. The graphs are based on mean parameter values obtained when the two-volume model was justified statistically.

A functional body fluid space peripheral to the sampled space. Our approach assumes that the volunteers handled the infused fluid either as a one-volume or a two-volume model in a hierarchical manner.

The current analyses usually identified $V_2$ when the volunteers were normovolemic. As hypovolemia reduced $k_c$, they were more likely to handle the fluid according to the two-volume model when they were hypovolemic. The frequent identification of $V_2$ is probably why the average total body fluid space expanded by infused fluid, approximately 10 l, is greater than reported previously. It would seem that infused fluid occupies a slightly larger body fluid space when the renal excretion of fluid is inhibited because of hypovolemia.

Some of the two-volume analyses were made by letting $k_c$ be determined by the urinary excretion instead of being estimated by the model. We believe this is justified when there is a high within-patient covariance between $k_c$ and $V_2$, indicating that the two parameters behave as one. This covariance problem typically occurs when the rate of elimination of fluid is very slow. In such cases, the experiment should be continued for a longer period. Simulation of theoretical data indicates that the parameters could be estimated confidently if the experiments had been continued for another 2 h. The long sampling time needed to analyze the kinetics accurately is apparent when the volume–time profile of $V_2$ is plotted (fig. 4, right), which shows that much excess fluid is still present at 3 h. A fixed $k_c$ is a useful, but not ideal, parameter to follow.

Table 3. Hemodynamics and Bioimpedance Data Representing the Patient Mean Value for All Measurements Done during Each Infusion Experiment

<table>
<thead>
<tr>
<th>Amount of Blood Withdrawn</th>
<th>0 ml</th>
<th>450 ml</th>
<th>900 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemodynamics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
<td>129.5 (1.1)</td>
<td>121.9 (0.7)</td>
<td>119.0 (1.0)</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>74.0 (1.0)</td>
<td>65.6 (0.5)</td>
<td>62.0 (0.6)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>63.9 (0.9)</td>
<td>60.2 (0.6)</td>
<td>67.6 (0.6)</td>
</tr>
<tr>
<td><strong>Bioimpedance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECF volume (L)</td>
<td>20.9 (0.5)</td>
<td>21.0 (0.5)</td>
<td>21.0 (0.5)</td>
</tr>
<tr>
<td>Total body water (L)</td>
<td>40.9 (1.1)</td>
<td>40.9 (1.0)</td>
<td>41.0 (1.3)</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>56.7 (1.1)</td>
<td>56.5 (1.4)</td>
<td>56.7 (1.8)</td>
</tr>
</tbody>
</table>

Values are mean (SEM). Hemodynamics were measured every 15 min and bioimpedance was measured when the infusion started (0 min), when it ended (30 min), and when the experiment had just been completed (180 min).

ECF = extracellular fluid.
approach to overcome this problem. Covariance has never been an issue in the one-volume model because all the infused fluid is usually eliminated within 2 h after the start of a 30-min infusion.

The results of the simulation experiments are presented in graphs (fig. 5) that can be used as nomograms to identify the infusion rates and infusion times required to restore and maintain normal blood volumes in hypovolemic persons. The frequent identification of $V_2$ prompted us to choose the two-volume model to construct these nomograms. They are based on the assumption that the plasma volume is a part of the primary fluid space ($V_1$), which is not unreasonable considering that the size of $V_1$ corresponds well to the expected plasma volume in normovolemic persons in the current and in previous investigations. Here $V_1$ even tended to decrease with the amount of blood withdrawn.

The following examples are given to acquaint readers with how the nomograms can be used. They were chosen to illustrate how somewhat different fluid regimens can be equally effective in restoring blood volume. To restore a blood volume reduced by 450 ml, an infusion rate of 60 ml/min during 15 min (total of 900 ml) or, alternatively, 30 ml/min during 40 min (1,200 ml) would be necessary. The additional fluid needed to maintain normal blood volume is then obtained from the right part of the nomograms. In the two examples given here, 27 ml/min (total of 1,215 ml) and 18 ml/min (total of 360 ml) would be required for the period for as long as 60 min after the treatment was started. Thus, 1,500 ml to 2,000 ml fluid is needed to replace an acute blood loss of 450 ml during 1 h, depending on how fast normal blood volumes are reached. Much larger amounts of fluid are needed to adequately replace a blood loss of 900 ml, but a slower rate of volume replacement always requires more fluid to attain normovolemia and less fluid to maintain it.

A few comments should be made about the nomograms. A simulated steady-state dilution by changing the infusion rate once after volume loading can be achieved only with the one-volume model, whereas the two-volume model yields a slightly concave form of the dilution–time curve. Therefore, the nomograms were designed to give the infusion rate required to restore
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Fig. 5. A nomogram showing the relation between the infusion rate and the infusion time (left) and the infusion rate required to maintain a steady state dilution 30 min later (right) when male volunteers given Ringer’s solution by intravenous infusion were normovolemic (top) and when 450 ml (middle) and 900 ml (bottom) blood had just been withdrawn. The (%) isobars show the predicted dilution of V1 (i.e., (V1 − V1)/V1), of which the plasma in the cubital vein is a part. The dilution required to obtain normovolemia is indicated by a thick irregular line in the middle and bottom graphs. The graphs are based on mean parameter values of the two-volume model as shown in table 1. The baseline blood volume was calculated from the weight and height of the volunteers using Nadler’s regression equation. Directions for using the nomogram:

1. Choose a desired dilution of the plasma (expressed as a percentage).
2. Using the left graph, start infusing Ringer’s solution at any combination of rate (y axis) and time (x axis) that meets the (%) isobar corresponding to the chosen dilution. To restore normal blood volume, choose the target dilution represented by the thick irregular line.
3. When the target dilution is found, take the horizontal to the right graph, along the same infusion rate line, to the line corresponding to the infusion time used. The steady state infusion rate is indicated by the vertical correlation (x axis).

exactly the maximum dilution 30 min after the end of the fast part of the infusion. A slightly slower infusion rate would be sufficient to restore exactly the maximum dilution after a longer period.

The nomograms do not show volume changes. Because V1 tended to decrease with the degree of hypovolemia, the volume change (V1 − V1) will increase to a lesser degree than the dilution (V1 − V1)/V1 in hypovolemia. This finding becomes apparent when figures 3 and 4 are compared. Finally, the nomograms are valid for crystalloid fluid replacement in healthy adult men in the awake state, but it is unknown whether they can be applied in trauma patients and under anesthesia. Under such conditions, the volume kinetics might be different. Adult women also require less fluid than men do to achieve the same dilution.

The results of the volume kinetic analysis may have been affected by hemodynamic factors. The arterial blood pressure was marginally, but still significantly, changed by blood withdrawal. The slowing of the heart rate is probably due to baroreceptor-mediated vagal stimulation, whereas the accelerated heart rate in moderate hypovolemia can be explained by endogenous sympathetic stimulation and ephedrine.

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The current study was done in such a way to minimize the effect of autotransfusion on the results. This compensatory mechanism counteracts hypovolemia by promoting fluid diffusion from the extracellular fluid spaces of the skin and muscles to the blood.\(^\text{19}\) Autotransfusion amounted to 150 ml after 30 min in moderate hypovolemia in another series of male volunteers,\(^\text{20}\) but the mechanism operates more slowly when less blood is withdrawn.\(^\text{21}\) Our data indicate that the autotransfusion amounted to approximately 100 ml (mild hypovolemia) and 150 ml (moderate hypovolemia) during blood withdrawal. However, the two sets of duplicate samples used to estimate the autotransfusion are not included in the figure for blood withdrawal, and a similar amount of blood was trapped in the tubes of the blood donor set. Therefore, the volunteers were still in a hypovolemic state that corresponded to the reported amount of withdrawn blood when the infusions began.

Autotransfusion during the infusions would be detected as a reduction of \(k_i\), and this can be discerned in the analyses based on the serum albumin concentration. The B-Hb data did not show the same clear decrease of \(k\) with the bleeding, although we must consider that a large \(k_i\) makes it more likely that a monoeponential curve fits the data as well as a biexponential curve.\(^\text{3}\) The reduction of \(k_i\) with the bleeding was not statistically significant, however, and our computer simulations show that \(k_i\) is a more important factor than \(k\) to explain the increased volume expansion of \(V_i\) in hypovolemic persons.

The volume kinetic analyses were based on an estimate of the baseline blood volume rather than being measured by a tracer substance. However, the blood volume was used only to correct the calculations for losses of hemoglobin and albumin induced by the blood sampling. Therefore, the parameters are relatively insensitive to errors in the estimate of blood volume. Reanalyses of the current experiments show that varying the blood volume between 80% and 120% of the figure that we used (a change by 50%) only induced a change in \(V_1\) of 1%, a change in \(k_i\) of 10%, and changes in \(k\) and \(V_2\) of 15%.

Another physiologic assumption is that the \(k_i\) becomes smaller when the participants are hypovolemic. The fixed parameter \(k_i\) is of limited importance when a large amount of fluid is infused, but hypovolemia strongly inhibits basal diuresis and recruits fluid from the cells by slowly increasing the plasma osmolality.\(^\text{13-15}\) In the current study, the use of a \(k_i\) of 0 ml/min instead of 0.8 ml/min would reduce \(V_1\) by 2% and increase \(V_2\) and \(k\) by 7%. As expected, the estimate of \(k_i\) would be affected most directly and become increased by 15%. This means that using an unchanged \(k_i\) during hypovolemia would exaggerate the differences in \(k\), found between our series of experiments.

The bioelectric impedance analysis was used as a noninvasive alternative to isotope dilution techniques to estimate the anatomic body fluid spaces. Bioimpedance analysis correlates well with more invasive approaches in healthy persons,\(^\text{8,9}\) although it may be difficult for it to detect acute dehydration.\(^\text{10}\) This method showed that the sizes of extracellular fluid and total body water volumes were practically identical in the three series of experiments. It was insensitive to blood loss but indicated an increase in the extracellular water volume when Ringer’s acetate solution was infused. The total body water we obtained, 54% of the body weight, corresponds closely with ethanol dilution,\(^\text{22}\) but deuterium usually gives values that are 5% greater.\(^\text{8,9}\) Only 50% to 70% of the extracellular water volume was expanded by the infused fluid, which conforms with the findings of a previous report.\(^\text{4}\) The greater figure was obtained with the serum albumin data, but it is probably less reliable because albumin may leak from the plasma into the interstitial space during volume loading.\(^\text{23}\)

In conclusion, a kinetic analysis of markers for the dilution of plasma shows that the volume effect of Ringer’s solution increases during hypovolemia. This can be explained by a reduction of the elimination rate constant while the size of the total body fluid space expanded by the infusion remained constant.

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References


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