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Volume Kinetics of Ringer Solution, Dextran 70, and Hypertonic Saline in Male Volunteers

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Background. **A knowledge of the distribution of different fluids given by intravenous infusion is basic to the understanding of the effects of fluid therapy. Therefore, a mathematical model was tested to analyze the volume kinetics of three types of fluids.**

Methods. **The authors infused 25 ml/kg of Ringer acetate solution, 5 ml/kg of 6% dextran 70 in 0.9% NaCl, and 3 ml/kg of 7.5% NaCl over 30 min in 8 male volunteers aged from 25 to 36 years (mean, 31 years) and measured the changes in total hemoglobin, serum albumin, and total blood water over time. The changes were expressed as fractioned dilution and then plotted against time. The curves were fitted to a one-volume and a two-volume model, which allowed an estimation of the size of the body fluid space expanded by the fluid (V) and the elimination rate constant (k_r) to be made.**

Results. **The changes in blood water concentration indicated a mean size of V of 5.9 l (± 0.8, SEM) for Ringer's solution, 2.6 (± 0.3) l for dextran, and 1.2 (± 0.1) l for hypertonic saline. The corresponding values of k_r were 94 (± 42), 12 (± 6), and 30 (± 4) ml/min, respectively. Blood hemoglobin indicated a degree of dilution similar to that indicated by blood water. Serum albumin indicated a more pronounced dilution, which resulted in a larger expandable volume and a greater mean square error for the curvefitting. The larger volume obtained for serum albumin can probably be explained by a loss of intravascular albumin into the tissues along with the infused fluid.**

Conclusions. **The distribution of intravenous fluids can be analyzed by a kinetic model adapted for fluid spaces, but slightly different results are obtained, depending on the marker used to indicate dilution of the primary fluid space. Analysis and simulation of plasma volume expansion by this model is a tool that can help the anesthetist to better plan fluid therapy. (Key words: Dextrans. Fluid therapy. Hemodilution. Pharmacokinetics. Saline solution, hypertonic. Serum albumin. Water/blood.)**

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INTRAVENOUS fluid therapy is an important part of patient care in surgery and trauma care. The volume expansion effect of the administered fluid is believed to be the therapeutic goal. This volume effect, however, is difficult to study. It often is taken as the change in distribution volume of radio-labeled or Evans blue-labeled albumin induced by volume loading.[1,2] This approach has been used, for example, to show that Ringer solution increases the blood volume by 20-25% of the given amount of fluid. Although such figures are of some practical value, they provide little insight into how volume changes over time. Further, the size of the fluid space(s) actually expanded by the fluid remains unclear.

In the present study, volunteers were given Ringer's solution, dextran, and hypertonic saline, and three markers of blood dilution were followed. Specifically, we followed the changes in blood hemoglobin, blood water, and serum albumin. The resultant curves were analyzed using a new kinetic model.[3] The purpose of fitting the data to a kinetic model is that this allows computer simulations to be made that predict the plasma volume expansion at any time during and after intravenous infusion of the fluid.

Materials and Methods

Eight healthy men aged 25-36 years (mean, 31 years) and weighing 69-100 kg (mean, 80 kg) participated in the study. The protocol was approved by the Local Ethics Committee, and the informed consent of all subjects was obtained.

Procedure

All subjects received three intravenous infusions, which were given in random order and on separate days at least 1 week apart. After an overnight fast, the volunteers rested comfortably on a bed, and at least 20 min of equilibration was allowed before the experiments started at 8:30 AM. The infusions consisted in 25 ml/kg of Ringer acetate solution (Pharmacia, Uppsala, Sweden), 5 ml/kg of 6% dextran 70 in 0.9% NaCl (Medisan, Uppsala, Sweden), and 3 ml/kg of 7.5% NaCl. The ionic content of the Ringer solution was (in mEq/l): Na, 130; K, 4; Ca, 2: Mg, 1; acetate, 30; and Cl, 110. The fluids were given at a constant rate over 30 min *via* an infusion pump (Flo-Gard 6201, Baxter Healthcare Ltd., Deerfield, IL).

Ringer solution and 6% dextran 70 are believed to increase the blood volume by 20–25%[1,2] and 100–120%,[4] respectively, of the infused volume. The fluid volumes we infused were balanced to have a similar volume effect in the blood. The volume of hypertonic saline was chosen to contain the same amount of sodium as the infused Ringer solution.

Measurements

Before any fluid was administered, a cubital vein of each arm was cannulated for the purpose of sampling blood and for infusion of fluid, respectively. Venous blood (10 ml) was collected every 5 min for 3 h. Before infusion, the first sample was drawn in duplicate, and the mean value was used in the calculations. These duplicate samples also were used to calculate the coefficient of variation for the analyzes performed.

The blood hemoglobin concentration (B-Hb) was measured on a Technicon H · 2 (Bayer, Tarrytown, NY) using colorimetry at 546 nm. The serum albumin concentration was measured by the bromcresol green method, followed by reflection spectrophotometry (Ektachem 250/950 IRC, Johnson & Johnson, Rochester, MN). Both of these analyses are standard in our hospital. The coefficient of variation was 1.3% for B-Hb and 3.0% for plasma albumin.

The water concentration of whole blood was calculated from the change in weight after drying. For this purpose, 1 ml of whole blood was transferred to preweighed glass beakers (10 g), weighed again, and then heated at 105°C overnight.[5] The water concentration was obtained as follows:

Blood water concentration = 1

− (water-free weight/weight of the fresh sample)

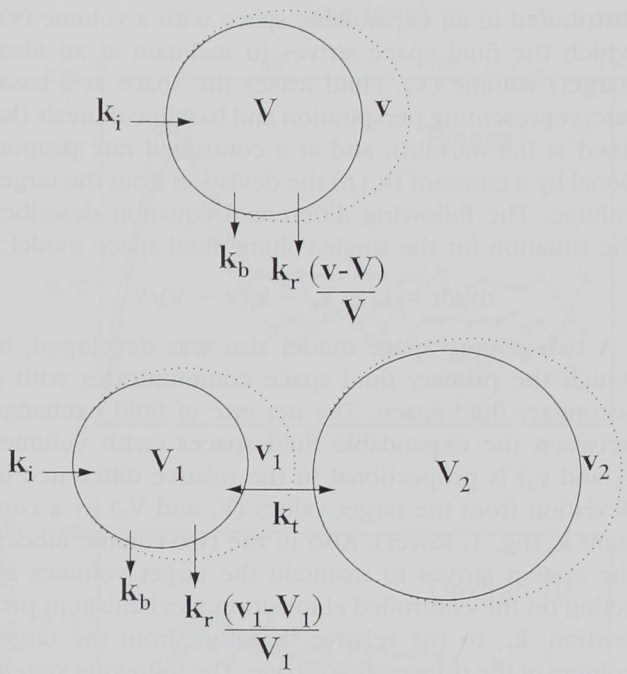

Fig. 1. Schematic drawing of the kinetic model used to calculate the size of the body fluid space expanded by intravenous infusion of fluid in humans.

The coefficient of variation of the measurement of water concentration of whole blood was 0.1%. The results obtained in mass/mass units were transformed to volume/volume units by assuming a specific weight (gravity) for blood of 1.055 at a water concentration of 800 ml/l.[6] In our experiments, the water concentration changed during the experiments and usually exceeded 800 ml/l. Therefore, a specific weight for blood was used, which considered the actual content of water. This adjustment of the specific weight was performed by using a linear regression equation, assuming that 1000 ml/l of water has a specific weight of 1.000 and that blood containing 800 ml/l of water has a specific weight of 1.055.

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

Calculations

The distribution of the fluid given by intravenous infusion was analyzed using volume-of-fluid-spaces kinetic models,[3] which can be summarized as follows (fig. 1, upper).

A fluid given by intravenous infusion at a rate k_i is

distributed in an expandable space with a volume (v), which the fluid space strives to maintain at an ideal (target) volume (V). Fluid leaves the space at a basal rate, representing perspiration and baseline diuresis (k_b, fixed at 0.8 ml/min), and at a controlled rate proportional by a constant (k_r) to the deviation from the target volume. The following differential equation describes the situation for the single-volume fluid space model:

$$dv/dt = k_i - k_b - k_r(v - V)/V$$

A two-volume space model also was developed, in which the primary fluid space communicates with a secondary 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_t (fig. 1, lower). Also in the two-volume model, the system strives to maintain the target volumes by acting on the controlled elimination mechanism in proportion, k_r, to the relative deviation from the target volume of the primary fluid space. The following system of differential equations describes the situation:

$$\frac{dv1}{dt} = k_i - k_b - k_r \frac{(v_1 - V_1)}{V_1} - k_t \left[\frac{(v_1 - V_1)}{V_1} - \frac{(v_2 - V_2)}{V_2} \right]$$

$$\frac{dv2}{dt} = k_t \left[\frac{(v_1 - V_1)}{V_1} - \frac{(v_2 - V_2)}{V_2} \right]$$

Mathematical solutions to these differential equations are presented in the Appendix.

The dilution of the plasma volume, *i.e.*, $(v_1 - V_1)/V_1$, was used to quantitate the fluid load. The plasma volume was chosen because the extracellular fluid, but not the erythrocytes, are expanded by the infused fluid. For this purpose, the data on plasma albumin were used directly. When the data on blood water and blood hemoglobin were analyzed, however, some intermediate calculations were needed. The dilution of the plasma volume was taken as the product of the dilution of the blood volume and (1 — hematocrit), where the hematocrit was assumed to decrease in proportion to the reduction of B-Hb. The blood volume during the study was obtained as the product of the hemodilution and the baseline blood volume, the latter being estimated from the weight and cube of height of the subjects.[7] The calculations for blood water were performed in the same way but using (1 — blood water) instead of B-Hb, as any dilution of B-Hb means that more water has been added to the system.

A correction for the loss of erythrocytes with the blood sampling always was made. The hemoglobin lost with the blood sampling was subsequently subtracted from the total hemoglobin mass, which was obtained as the product of the baseline B-Hb and the blood volume. A correction for the loss of extracellular fluid associated with the blood sampling also was made by setting k_b to 0.8 ml/min instead of 0.5 ml/min, which is an approximation of the basal fluid loss from the expandable fluid space(s) in the fasting state of adults. Despite the fact that k_b is reported in terms of flow (ml/min), it has little in common with the clearance concept — k_b is of zero order and is not directly related to the other constants in the model.

Estimates and their standard deviations of the unknown parameters in the fluid-space models were obtained by using nonlinear least-squares regression (modified Gauss-Newton method) to fit the dilution-time profiles into the equations shown in the Appendix. The iterations stopped when all parameters had changed less than 0.001 (0.1%) in two iterations. Calculations were performed on a Macintosh computer (Cupertino, CA) using Matlab version 4.2 (Math Works Inc., Notich, MA).

In the single-volume model, V and k_r were calculated. The two-fluid space model gives V_1, V_2, k_t, and k_r. A partial F test was applied to the residual errors (mean square error [MSQ]) to suggest the most appropriate model for presentation.[8] The two-fluid space model was rejected in a few analyses in which it was statistically justified because the correlation matrix showed a correlation of 0.99 between V_2, k_t, and k_r, respectively. Such a high degree of correlation implies that these three parameters behaved as one parameter.

The results are expressed as the mean and the SEM. The statistical evaluation was performed using also one-way analysis of variance (ANOVA), repeated-measures ANOVA followed by the Newman-Keul test. $P < 0.05$ was considered significant.

Results

The most pronounced changes in the three markers for dilution occurred during the infusion of Ringer solution (25 ml/kg). The dilution associated with dextran (5 ml/kg) was comparable with that of hypertonic saline

(3 ml/kg of 7.5% NaCl), but the effect lasted longer (fig. 2). The changes in the concentrations of blood hemoglobin and blood water correlated closely throughout the experiments. Plasma albumin became more diluted and indicated a more pronounced expansion of the plasma volume (fig. 2). This difference between the markers was most apparent when hypertonic NaCl was infused.

The dilution-time curves of the three markers were then corrected for blood sampling and analyzed according to the fluid space models (fig. 3). The results show that the two-volume space model could be justified statistically for some of the experiments with Ringer solution and hypertonic saline, whereas this was not the case for the dextran infusions (tables 1, 2, and 3). The dilution of the peripheral fluid space (v_2) could be calculated in the experiments in which the two-fluid space model was appropriate (fig. 4).

The statistically justified model (one- or two-volume model) was used in each experiment for further comparisons between the volumes and kinetic constants (table 4). The size of the total expandable volume was largest for Ringer solution, intermediate for dextran, and smallest for hypertonic saline. For Ringer solution, the expandable volume was larger when the dilution was indicated by serum albumin as compared with blood water ($P < 0.01$) and blood hemoglobin ($P < 0.05$). The trend was the same for dextran and hypertonic saline, but the difference did not reach statistical significance. In contrast, serum albumin yielded an overall lower estimate of k_r than blood hemoglobin ($P < 0.05$).

The MSQ for the statistically justified model usually was lowest when the curve-fit was based on the blood water dilution, but it was significantly lower only when being compared with the data on serum albumin in the dextran and hypertonic saline experiments.

Discussion

Pharmacokinetic analysis and simulation is the standard approach to create guidelines for pharmacologic management during anesthesia. Such tools have not previously been available in fluid therapy. To our knowledge, the kinetic model used in the present study is the first to allow analysis of the distribution of the volume of an intravenous infusion *in vivo*. A single-volume and a two-volume kinetic model have been developed because it is likely that fluid can be distributed at different rates to at least two expandable fluid spaces in the body.

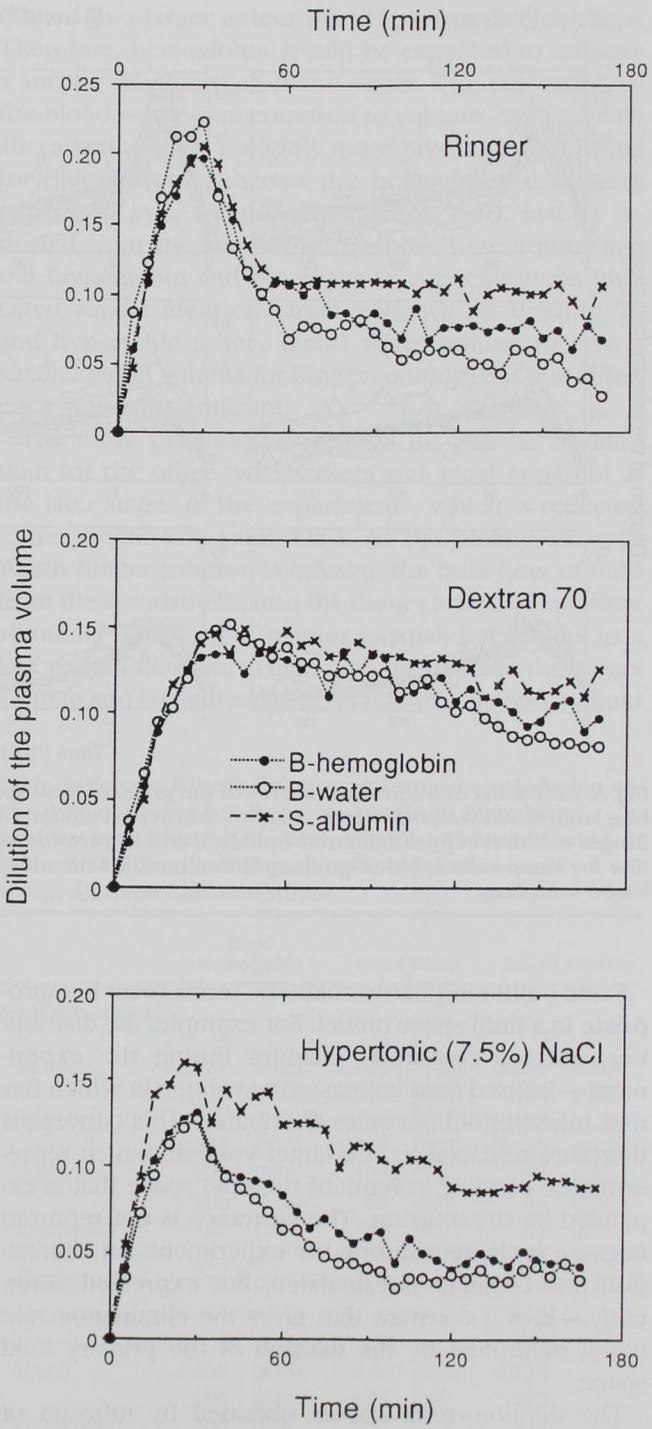

Fig. 2. The blood hemoglobin (B-hemoglobin), blood water (B-water), and serum albumin (S-albumin) concentrations used as markers to indicate the dilution of the plasma volume during intravenous infusion of 25 ml/kg of Ringer solution (upper), 5 ml/kg of dextran 70 (middle), and 3 ml/kg of 7.5% saline (lower) over 30 min in 8 male volunteers. Data are mean values, and correction for blood sampling was not made.

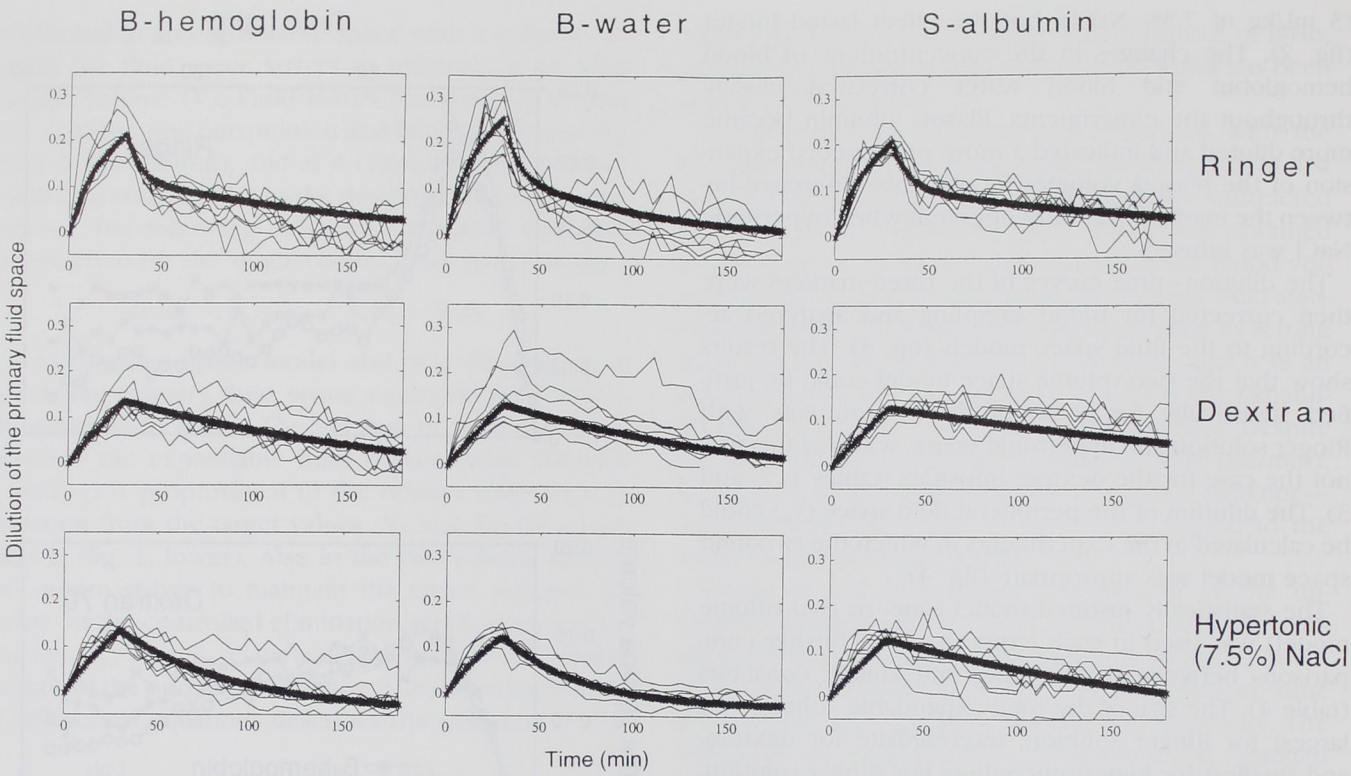

Fig. 3. Individual dilution–time curves of the primary fluid space (fine lines) when based on the blood hemoglobin (B-hemoglobin; left), blood water (B-water; middle), and serum albumin (S-albumin) concentrations (right) during intravenous infusion of Ringer solution (upper), dextran (middle), and hypertonic saline (lower). The thick line in each graph is the model-predicted line for these values, based on the predominant kinetic model (one-volume or two-volume model). All data were corrected for blood sampling.

Some common pharmacokinetic terms seem inappropriate in a fluid space model. For example, the distribution volume constantly changes during the experiment — infused fluid increases the volume in which further infused fluid becomes distributed. This concept is therefore replaced by the target volume, which represents the baseline volume of the fluid space that is expanded by the infusion. The clearance is not reported because it changes during the experiment. An elimination rate constant is calculated, but expressed differently — k_r is a constant that gives the elimination rate when multiplied by the dilution of the primary fluid space.

The dilution-time curves obtained by infusion of Ringer solution, dextran 70, and hypertonic saline indicate how the plasma expansion of these fluids change over time. Inspection alone of these curves tells an important story about the magnitude of change and its time course. The dilution-time profiles appeared to be predictable, which is the basis for fitting them into the fluid space models. Slightly different results were obtained, however, depending on the marker used to indicate dilution. This can be explained, in part, by the variable precision with which these markers were measured. The results of the fluid space model analyses are stable when random errors are imposed on the indicator of plasma dilution. The chief exception is the size of the secondary fluid space (V_2), which usually becomes larger with poorer precision.[3] Differences in results also can be explained by the fact that the dilution-time curves look different depending on the marker used.

Two of our markers are available in routine laboratories for blood chemistry, whereas blood water finds little application in modern medicine. It is performed by careful weighing of blood before and after desiccation. The blood water analysis is time-consuming, but the precision is high, which is reflected in the relatively small MSQ obtained when such data were used in the fluid space model. Blood water also is attractive to use from a theoretical point of view because the purpose

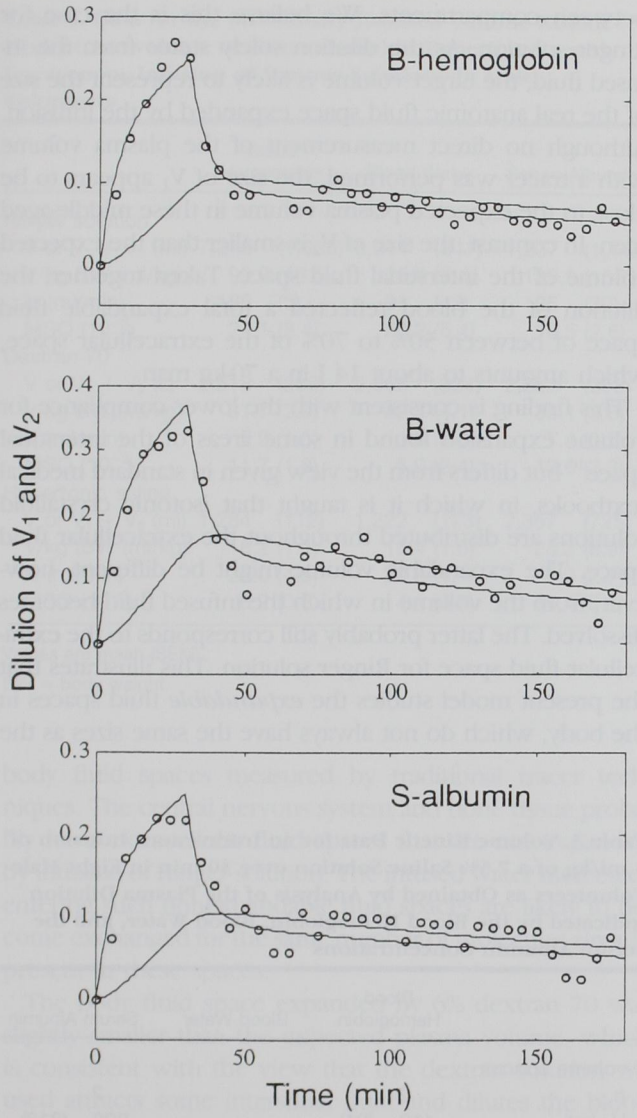

Fig. 4. Representative graphic output of the volume kinetic analysis in one male volunteer in whom the blood hemoglobin (B-hemoglobin; upper), blood water (B-water; middle), and serum albumin (S-albumin; lower) concentrations were used as markers of dilution during and after an intravenous infusion of Ringer solution. The measured dilution (circles) and the model predicted dilution–time curve for the primary fluid space (upper line during infusion) and the secondary fluid space are shown.

of fluid loading is to increase the water content (*i.e.*, the volume) of a fluid space.

The hemoglobin level correlates inversely with the water concentration of the blood during infusion experiments, provided that other solid components of the blood are changed to the same extent. This was clearly not the case with serum albumin, which usually was diluted to a larger extent than the other two markers. Therefore, hemoglobin would be expected to indicate a smaller dilution than blood water. The correction of the blood water concentration to volume-volume data also acted to yield a slightly more pronounced dilution for blood water, whereas the hemoglobin data were expressed in a weight-volume unit (g/l), just as reported from the laboratory. Despite these arguments, the hemoglobin and blood water concentrations indicated almost identical target volumes for dextran 70 and hypertonic saline. Blood water tended to give a smaller target volume for Ringer solution, but this difference was not significant.

The more pronounced dilution for plasma albumin than for the other two markers was most apparent at the later stages of the experiments, which is reflected in an overall low value for k_r in the kinetic analysis. When Ringer solution is infused, the bulk flow of fluid from the bloodstream into the tissues brings along some albumin.[9] This loss of marker is small but results in a late excess dilution, which acts to increase the target volume and facilitates the detection of a secondary fluid

Table 1. Volume Kinetic Data for an Intravenous Infusion of 25 ml/kg of Ringer Solution over 30 min in Eight Male Volunteers as Obtained by Analysis of the Plasma Dilution Indicated by the Blood Hemoblogin, Blood Water, and Serum Albumin Concentrations

	Blood Hemoglobin		Blood Water		Serum Albumin	
2-volume spaces						
n	4		5		7	
V_1 (ml)	3,327	(438)	2,769	(445)	3,851	(395)
	1,175	(463)	569	(130)	880	(126)
V_2 (ml)	6,926	(2,594)	4,443	(1,054)	8,138	(1,271)
	1,805	(375)	1,039	(256)	2,122	(372)
k_t (ml/min)	295	(59)	190	(34)	283	(38)
	205	(113)	66	(31)	97	(28)
k_r (ml/min)	91	(15)	110	(28)	81	(22)
	11	(2)	9	(1)	15	(3)
MSQ (10^{-3})	12.7	(2.8)	14.9	(4.3)	14.4	(1.8)
1-volume space						
n	4		3		1	
V (ml)	4,500	(875)	3,834	(494)	5,729	
	906	(541)	377	(66)	463	
k_r (ml/min)	280	(81)	180	(11)	114	
	36	(22)	13	(3)	8	
MSQ (10^{-3})	35.4	(12.7)	28.9	(12.4)	31.0	

The first line for each parameter gives the estimate and second line gives its standard error. In parentheses after each mean value is the variability for the group expressed as the standard error of the mean (SEM).

MSQ = mean square error.

Table 2. Volume Kinetic Data for an Intravenous Infusion of 5 ml/kg of 6% Dextran 70 over 30 min in Eight Male Volunteers as Obtained by Analysis of the Plasma Dilution Indicated by the Blood Hemoglobin, Blood Water, and Serum Albumin Concentrations

	Blood Hemoglobin	Blood Water	Serum Albumin
n	8	8	8
V (ml)	2,518 (268)	2,568 (334)	2,821 (258)
	159 (33)	149 (48)	399 (224)
k_r (ml/min)	14.9 (4.8)	23.5 (9.7)	7.4 (3.5)
	1.8 (0.3)	2.5 (1.3)	1.8 (0.3)
MSQ (10^{-3})	11.7 (1.8)	6.9 (2.4)	13.6 (3.3)

Values are mean (SEM). In all cases, the one-fluid space model was selected for presentation. The first line for each parameter gives the estimate and second line gives the standard error.

space. In our study, albumin indicated a secondary fluid space in seven of the eight experiments with Ringer solution. The size of this space should be regarded with caution because of the probable loss of marker.

The kinetic data presented in this study can be used to simulate volume expansion by computer. Such simulations open up the possibility of finding alternative fluid regimens that all reach a predetermined expansion of the plasma volume. For example, imagine that we want to obtain a plasma dilution of 10% within 20 min, and also that we want to maintain this dilution for another 20 min. (This is the same as increasing the blood volume by about 5%, depending somewhat on the hematocrit). In a healthy man, this goal can be reached by first infusing Ringer solution at a rate of 48 ml/min during 20 min and then maintaining steady state by reducing the rate to 20 ml/min. If we use dextran 70, the corresponding rates would be 14 and 1.5 ml/min, respectively. Finally, the rates would be 8 and 3 ml/min if hypertonic NaCl is given. These simulations are based on the dilution of blood hemoglobin, and the data for the optimal kinetic model are used (table 4). The infusion rates required to reach the goal are lower if the patient handles the fluid according to the two-volume model, but these differences are not great. Our example illustrates that the volume kinetic models allow the anesthetist to calculate how a desired volume expansion can be reached by varying the infusion rate, the infusion time, or the type of fluid. At present, however, these calculations are applicable only to healthy men who are not under surgical stress and do not bleed. The kinetic volumes and constants might be different under conditions that were not studied in the present study.

Another question is whether volume kinetics provide insight into real volumes and rates of exchange of fluid between compartments. We believe this is the case for Ringer solution. As the dilution solely stems from the infused fluid, the target volume is likely to represent the size of the real anatomic fluid space expanded by the infusion. Although no direct measurement of the plasma volume with a tracer was performed, the size of V_1 appears to be close to the expected plasma volume in these middle-aged men. In contrast, the size of V_2 is smaller than the expected volume of the interstitial fluid space. Taken together, the dilution of the blood reflected a total expandable fluid space of between 50% to 70% of the extracellular space, which amounts to about 14 l in a 70-kg man.

This finding is consistent with the lower compliance for volume expansion found in some areas of the interstitial space[10] but differs from the view given in standard medical textbooks, in which it is taught that isotonic crystalloid solutions are distributed throughout the extracellular fluid space. The expandable volume might be different, however, from the volume in which the infused fluid becomes dissolved. The latter probably still corresponds to the extracellular fluid space for Ringer solution. This illustrates that the present model studies the *expandable* fluid spaces in the body, which do not always have the same sizes as the

Table 3. Volume Kinetic Data for an Intravenous Infusion of 3 ml/kg of a 7.5% Saline Solution over 30 min in Eight Male Volunteers as Obtained by Analysis of the Plasma Dilution Indicated by the Blood Hemoglobin, Blood Water, and the Serum Albumin Concentrations

	Blood Hemoglobin	Blood Water	Serum Albumin
2-volume spaces			
n	2		2
V_1 (ml)	410 (21)		908 (319)
	189 (60)		190 (68)
V_2 (ml)	741 (214)		4,322 (1,581)
	177 (48)		3,385 (2,818)
k_t (ml/min)	59 (1)		77 (25)
	40 (21)		22 (7)
k_r (ml/min)	10.0 (1.8)		−4.5 (8.9)
	1.0 (0.2)		12.0 (7.9)
MSQ (10^{-3})	6.9 (0.7)		6.1 (1.5)
1-volume space			
n	6	8	6
V (L)	1,328 (140)	1,222 (123)	1,399 (88)
	90 (12)	71 (11)	103 (20)
k_r (ml/min)	23.4 (5.3)	30.3 (4.1)	5.4 (1.9)
	2.0 (0.3)	1.8 (0.3)	1.1 (0.3)
MSQ (10^{-3})	8.7 (0.9)	4.4 (0.7)	20.5 (6.1)

Values are mean (SEM). The first line for each parameter gives the estimate and second line gives the standard error.

Table 4. Data for the Statistically Justified Volume Kinetic Model (One-volume or Two-volume) in Experiments with Intravenous Infusion of Various Solutions in Male Volunteers

	Blood Hemoglobin	Blood Water	Serum Albumin
Ringer solution			
V or $V_1 + V_2$ (ml)	7,376 (1,623)	5,944 (841)	11,207 (1,448)
V/kg BW (ml/kg)	92.2 (18.5)	73.8 (8.4)	139.9 (15.7)
k_r (ml/min)	186 (5)	94 (42)	85 (20)
MSQ (10^{-3})	24.1 (8.4)	20.2 (5.4)	16.5 (2.6)
Dextran 70			
V or $V_1 + V_2$ (L)	2,518 (268)	2,568 (334)	2,822 (258)
V/kg BW (ml/kg)	31.7 (2.9)	32.8 (4.1)	36.1 (3.6)
k_r (ml/min)	5.9 (1.8)	11.8 (6.0)	7.4 (3.5)
MSQ (10^{-3})	11.7 (1.8)	6.9 (2.4)	13.6 (3.3)
Hypertonic saline			
V or $V_1 + V_2$ (ml)	1,284 (112)	1,222 (123)	2,357 (725)
V/kg (BW (ml/kg)	16.2 (1.1)	15.4 (1.6)	28.2 (6.9)
k_r (ml/min)	20.0 (4.5)	30.3 (4.1)	2.9 (2.7)
MSQ (10^{-3})	8.2 (0.8)	4.4 (0.7)	14.4 (5.1)

Values are mean (SEM).

BW = body weight.

body fluid spaces measured by traditional tracer techniques. The central nervous system and bone tissue probably have extracellular fluid spaces that are not expanded by infusion of Ringer solution. The infused water molecules entering such nonexpandable fluid spaces are likely to become exchanged for the same number of molecules already present in these spaces.

The body fluid space expanded by 6% dextran 70 was slightly smaller than the expected plasma volume, which is consistent with the view that the dextran solution we used attracts some interstitial fluid and dilutes the blood by more fluid than its own volume.[4] The reduction of the expandable fluid space resulting from diffusion of water from the interstitial fluid space to the blood is even more apparent for hypertonic saline. Most of the volume effect of hypertonic saline is exerted by intracellular fluid recruited by osmosis. The curve-fitting also yielded some cases of a negative k_r, which implies that fluid recruited to the expandable fluid space from nonexpandable portions of the body water exceeded the rate of elimination also during the postinfusional phase of the hypertonic saline experiments.

It should be noted that our estimation of plasma dilution from whole blood data assumes a stable ratio between the hemoglobin concentration and the hematocrit. The hematocrit *per se* indicates dilution in too rough steps to be used for volume kinetic analysis, but it should be included as a complement to detect major osmotic shifts during experiments. There is no consistent change in the hemoglobin-hematocrit ratio when an isotonic solution, such as Ringer solution and dextran, is infused. The excess albumin dilution during the experiments with hypertonic saline, however, might be explained by an osmolality-induced shrinkage of erythrocytes.

In conclusion, dilution-time profiles can be used to analyze the kinetics of Ringer solution, dextran 70, and hypertonic saline *in vivo*. The blood hemoglobin and blood water concentrations are useful markers of dilution during infusion of the two isotonic solutions, whereas plasma albumin is probably more suitable when hypertonic saline is given.

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Appendix

The mathematical models are linear differential equations with constant coefficients and their solutions can be given analytically in different forms. The single fluid space model (Eqn. 1) is easily solved as a monoexponential solution. During (d) infusion, it is

$$w_d(t) = [(k_i - k_b)/k_r](1 - e^{-k_r t/V}), \quad 0 \le t \le t_1$$

and after (a) infusion

$$w_a(t) = (-k_b/k_r)(1 - e^{-k_r(t-t_1)/V}) + W_d(t_1)e^{-k_r(t-t_1)/V}, \quad t_1 \le t \le \infty$$

where w(t) is the dilution (v(t)-V)/V.

The solution of the two-fluid-space model, (Eqn. 2) and (Eqn. 3), can be presented in different ways. The first form of the solution based on the matrix exponential e^{At} is a direct generalization of the former solution. During infusion (d) we have

$$\begin{pmatrix} w_{1d}(t) \\ w_{2d}(t) \end{pmatrix} = [(k_i - k_b)/k_r](I - e^{At}) \begin{pmatrix} 1 \\ 1 \end{pmatrix} \quad 0 \le t \le t_1$$

and after infusion

$$\begin{pmatrix} w_{1a}(t) \\ w_{2a}(t) \end{pmatrix} = (-k_b/k_r)(I - e^{A(t-t_1)}) \begin{pmatrix} 1 \\ 1 \end{pmatrix} + e^{A(t-t_1)} \begin{pmatrix} w_{1d}(t_1) \\ w_{2d}(t_1) \end{pmatrix} \quad t_1 \le t \le \infty$$

where the matrix A is

$$A = \begin{pmatrix} -(k_r + k_t)/V_1 & k_t/V_1 \\ k_t/V_2 & -k_t/V_2 \end{pmatrix}$$

This form is well suited for numerical computation of the solution of (Eqn. 2 and 3) with, for example, the mathematical program Mat-

lab, which has the matrix exponential e^{At} implemented as a standard function.

In a second form of presenting the two-fluid space solution, the biexponential form is clearly seen:

$$w_1(t) = Q_1e^{Xt} + Q_2e^{Yt} + Q_3$$

$$w_2(t) = Q_4e^{Xt} + Q_5e^{Yt} + Q_6$$

where X and Y are eigenvalues of A, *i.e.*,

$$0.5\left[\frac{-(k_r + k_t)}{V_1} - \frac{k_t}{V_2} \pm \sqrt{\left(\frac{k_r + k_t}{V_1} - \frac{k_t}{V_2}\right)^2 + \frac{4k_t^2}{V_1V_2}}\right]$$

and the coefficients Q_1, Q_1, Q_3 ... are nonlinear functions in the parameters k_r, k_t, k_l, k_b, V_1, and V_2. The analytical form of these coefficients are different during infusion and after infusion.[3] Both solutions to the two-fluid space model give the same parameter estimations, but the former approach was used in the present study because it is more easy to develop when making simulation experiments with variable infusion rates.

References

1. Lamke L-O, Liljedahl S-O: Plasma volume changes after infusion of various plasma expanders. Resuscitation 1976; 5:93–102

2. Moore FD, Dagher FJ, Boyden CM, Lee CJ, Lyons JH: Hemorrhage in normal man: I. Distribution and dispersal of saline infusions following acute blood loss. Ann Surg 1966: 163:485–504

3. Ståhle L, Nilsson A, Hahn RG: Modelling the volume of expandable body fluid spaces during i.v. fluid therapy. Br J Anaesth 1997; 78:138–43

4. Hint H: The pharmacology of dextran and the physiological background for the clinical use of Rheomacrodex and Macrodex. Acta Anaesthesiol Belg 1968; 2:119–38

5. De Jong GMT, Huizenga JR, Wolthers BG, Jansen HG, Uges DA, Hindriks FR, Gips CH: Comparison of the precision of seven analytical methods for the H20 concentration in human serum and urine. Clin Chim Acta 1987; 166:187–94

6. Jones AW, Hahn RG, Stalberg HP: Determination of total body water by ethanol dilution: Importance of concentration units used in the calculations. Clin Sci 1991; 81:701–2

7. Nadler SB, Hidalgo JU, Bloch T: Prediction of blood volume in normal human adults. Surgery 1962; 51:224–32

8. Motulsky HJ, Ransnäs LA: Fitting curves to data using nonlinear regression: A practical and nonmathematical review. FASEB J 1987; 1:365–74

9. Renkin WM, Rew K, Wong M, O'Loughlin D, Sibley L: Influence of saline infusion on blood-tissue albumin transport. Am J Physiol 1989; 257:H525–33

10. Aukland K, Reed RK: Interstitial-lymphatic mechanisms in the control of extracellular fluid volume. Physiol Rev 1993; 73:1–78