Original Article

The kinetics of isotonic and hypertonic resuscitation fluids is dependent on the sizes of the body fluid volumes

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Abstract

Background and Aims: The extracellular and intracellular fluid volumes (ECV and ICV) vary not only with age, gender, and body weight but also with the habitual intake of water. The present study examines whether the baseline variations in the ECV and ICV change the distribution and elimination of subsequently given infusion fluids.

Material and Methods: Twenty healthy male volunteers underwent 50 infusion experiments with crystalloid fluid for which the fluid volume kinetics was calculated based on frequent measurements of the hemodilution using mixed-effects modeling software. The results were compared with the ECV and ICV measured with multifrequency bioimpedance analysis before each infusion started. The fluids were given over 30 minutes and comprised 25 mL/kg Ringer's acetate (N = 20), Ringer's lactate, 5 mL/kg 7.5% saline, and 3 mL/kg 7.5% saline in 6% dextran 70 (these fluids, N = 10).

Results: A large ICV was associated with a small extravascular accumulation of infused fluid, which increased the plasma volume expansion and the urinary excretion. With hypertonic fluid, a large ECV greatly accelerated urinary excretion. The body weight did not serve as a covariate in the kinetic models. Albumin was recruited to the plasma during infusion of both types of fluid. The hypertonic fluids served as diuretics. The infused excess sodium and osmolality were distributed over a 35% larger space than the sum of the ECV and ICV.

Conclusion: A large ICV reduced the rate of distribution of Ringer's solution, whereas a large ECV accelerated the excretion of hypertonic saline.

Keywords: Body water, crystalloid solutions, extracellular space, hypertonic, intracellular space, pharmacokinetics, physiology, saline solution

Introduction

The body has a high content of water, accounting for approximately 50% of the body weight in adult women and up to 60% in males.[1,2] The absolute sizes of the body fluid volumes vary with age, gender, and body weight.[3] Acute dehydration decreases these volumes, while chronic dehydration due to habitual low intake of water makes the kidneys prone to overcompensation whereby the intracellular fluid volume (ICV) increases.[4]

Intravenous fluid therapy with a crystalloid solution is a common intervention in hospitals. This type of fluid undergoes a clearly separated distribution and elimination phase that is dependent on the physiological situation. Both phases can be simultaneously quantified by volume kinetic analysis, which is a pharmacokinetic approach based on frequent measurements of the fluid-induced hemodilution.[5] Such an infusion abruptly changes the extracellular fluid volume (ECV) and possibly also the ICV. However, if differences in the sizes of the ECV and ICV at the starting point, that is, *before* the therapy begins,

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influence the subsequent distribution, and elimination of an infusion fluid is not known.

The present report explores the potential relationships between the ICV and ECV, as measured by bioimpedance, and the volume kinetics of nearly isotonic infusion fluids (Ringer's acetate and Ringer's lactate), hypertonic 7.5% saline (HS), and 7.5% saline in 6% dextran (HSD).[6,7] The two Ringer fluids are widely used for plasma volume expansion in hospital care, whereas the two hypertonic saline preparations are resuscitation fluids used in prehospital rescue settings.[6,7] The aim of the analysis was to examine whether the sizes of the body fluid volumes influence the effectiveness of these infusion fluids in expanding the plasma volume. The *primary hypothesis* was that smaller body fluid sizes promote more effective plasma volume expansion. The *secondary hypothesis* was that the total body water (TBW) correlates with the distribution volume of the sodium that is infused with the hypertonic fluid. Confounding influences of age and gender were avoided by analyzing experiments performed only in healthy males of a relatively limited age span.

Material and Methods

The report is a retrospective analysis of two studies of hemodilution in euvolemic volunteers.[8,9] These studies were approved by the Ethics Committee of Huddinge Hospital (Dnr. 54/95 and 228/98, Chairmen Lennart Kaijser and Ola Eiken), and informed consent was obtained from all participants. Ten healthy male volunteers participated in a total of 50 intravenous infusion experiments. The treatments consisted of 20 infusions of 25 mL/kg Ringer's acetate (Baxter, ionic content in mEq/L; Na 130, K 4, Ca 2, Cl 110, acetate 30; osmolality 273 mOsm/L) and 10 infusions each of Ringer's lactate (Baxter, acetate replaced by lactate 28), 5 mL/kg of 7.5% saline, and 3 mL/kg of 7.5% saline in 6% dextran. The fluids used in the latter series were administered in random order. All infusions were administered at a constant rate over 30 minutes by using an infusion pump.

The volunteers had a light breakfast consisting of one glass of water or milk and one sandwich at least 2 hours before the infusion, which began at 9.00 a.m. They voided and were weighed just before the infusion started. The subjects rested comfortably on a bed, were covered with blankets, and venous cannulas were inserted into the antecubital veins in both arms. One was used for infusion and the other for blood sampling. A recumbent equilibration period of 30 minutes was allowed before the experiments were initiated.

When an infusion had started, venous blood (3 mL) was drawn every 5 minutes for 2 hours and then every 10 minutes for the subsequent 2 hours for a total of 37 samples and approximately 100 mL of blood. The blood hemoglobin (Hb) concentration was analyzed for every sample, the hematocrit only on the first sample, and serum sodium and serum osmolality were measured every 10 to 30 minutes at the hospital's certified clinical chemistry laboratory. The monitoring equipment consisted of electrocardiography, noninvasive arterial pressure, and pulse oximetry.

Body fluid volumes

The volumes of the ECV and TBW were measured just before each infusion was initiated by multifrequency bioelectrical impedance (Xitron 400B Bioimpedance Spectrum Analyzer, Xitron Technologies Inc., San Diego, CA, USA). This apparatus calculates these volumes by applying a series of 50 currents of different frequencies between electrodes affixed to the dorsum of one hand and one foot. The spectrum of the signal is fitted to a structural model that separates the material from its component parts and then mathematically relates the terms of this model to the sizes of the ECV and TBW. The mean of three consecutive measurements was recorded, and ICV was taken as the difference between the two measured volumes. Each measurement is painless and requires approximately 2 minutes for completion.

Kinetic analysis

Population (mixed effects) kinetics is an industrial standard tool for evaluating and recommending dosing regimens for drugs with regard to individual-specific factors, such as age, gender, and body weight.[10] The volume kinetic method is a modification of drug pharmacokinetics in that the compartments have expandable walls. A benefit is that dynamic events can be studied, which is difficult with radioactive tracer methods. Just like drugs, infusion fluids can be studied by kinetic approaches.[5] Volume kinetics is based on dilution of the blood Hb concentration, which is the inverse of the blood water concentration.[5] Infusion fluids contain almost exclusively water; therefore, Hb changes are an index of the infused water volume that rapidly equilibrates with the circulating blood. When electrolytes are measured, the volume kinetic analysis measures the distribution volume of the electrolyte in question.[11]

Ringer's solutions. A two-volume kinetic model created to reflect body physiology was used for the analysis of the Ringer's solutions. Fluid was infused at a rate R_0 into an expandable body fluid space V_c (the plasma), which becomes expanded to v_c. Distribution and elimination are governed by the three rate constants: k_{12} for flow from V_c to a peripheral space V_t (the interstitial space, which then becomes expanded to v_t), k_{21} for flow in the opposite direction (from interstitium to plasma), and k_{10} for elimination by urinary excretion. A fourth rate constant, k_b, represents the "third-space" elimination, that is, for fluid not detected as urine.[12]

Hypertonic fluids. The same model was used for the hypertonic fluids, except that the infused surplus of sodium ions caused osmotic-driven recruitment of water from the ICV to the ECV. Mass balance calculations have shown that each mL of 7.5% saline translocates 4.9 mL of water from the ICV to ECV.[8]

Plasma sodium and serum osmolality. A one-volume model was applied to estimate the volume of distribution of the surplus of sodium infused with the hypertonic fluids. The elimination was set to the measured urinary excretion of sodium and osmolality.

Calculations. The key equations for the two-volume model are the following:

$$dv_c/dt = R_0 - k_{12}(v_c - V_c) + k_{21}(v_t - V_t) - k_{10}(v_c - V_c) - k_b(v_c - V_c);$$

$$dv_t/dt = k_{12}(v_c - V_c) - k_{21}(v_t - V_t);$$

$$dU/dt = k_{10}(v_c - V_c);$$

$$(v_c - V_c)/V_c = [(Hb_o/Hb) - 1)]/(1 - \text{hematocrit}_o);$$

Table 1: Details on the infusion fluids and their excretion

Variable	Lactated and acetated Ringer's	HS	HSD	Significance level (ANOVA)
Infused Volume, mL	2,017 (202)*	411 (43)	242 (24)	*P*<0.001
Sodium, mmol	242 (26)	527 (55)*	318 (40)*	*P*<0.001
Potassium, mmol	8 (1)*	0	0	*P*<0.001
Osmoles, mosmol	555 (56)*	1,054 (110)	620 (62)	*P*<0.001
Excreted				
Volume, mL	1,135 (390)	1,010 (555)	721 (245)	*P*=0.07
Sodium, mmol	109 (46) *	192 (74)	259 (64)	*P*<0.02
Potassium, mmol	26 (12) *	59 (25)	44 (18)	*P*<0.01
Osmoles, mosmol	376 (114)	527 (55)	310 (31)	*P*<0.06
Excreted/infused				
Volume, ratio	0.6 (0.2)*	2.6 (1.5)	3.0 (1.0)	*P*<0.001
Sodium, ratio	0.4 (0.2)	0.4 (0.2)	0.9 (0.6)*	*P*<0.04
Osmoles, ratio	0.7 (0.2)	0.5 (0.1)	0.9 (0.3)**	*P*=0.09

*Significantly different from the others by * P< 0.05 or ** P< 0.01 (Scheffé post hoc ANOVA) HS=hypertonic 7.5% saline; HSD=hypertonic 7.5% saline in 6% dextran; ANOVA=analysis of variance*

Table 2: Body fluid volumes in all 50 experiments and the population kinetic parameters for the analysis of sodium and osmolality kinetics of the 20 infusions of hypertonic fluid (7.5% saline and 7.5% saline in 6% dextran 70)

	Covariate	Best estimate	95% CI	CV%
Body fluid volumes				
ECV (L)		20.3	19.7-20.8	9.9
ICV (L)		18.5	17.9-19.2	12.6
TBW (L)		38.8	37.7-39.9	10.3
ECV/body weight (L/kg)		0.254	0.248-0.260	8.7
ICV/body weight (L/kg)		0.233	0.224-0.242	13.3
TBW/body weight (L/kg)		0.487	0.473-0.502	10.3
Sodium kinetics				
tvV_c (L)	-	52.1	47.4-56.8	4.6
tvk_{10} (10^{-3} min^{-1})	-	2.64	1.70-3.57	18.1
Covariate effects				
V_c	TBW	1.50	0.90-2.10	20.2
k_{10}	HSD	0.59	0.18-1.00	35.3
Osmolality kinetics				
tvV_c (L)	-	54.3	46.7-61.8	7.0
tvk_{10} (10^{-3} min^{-1})	-	2.15	1.12-3.17	24.2
Covariate effects				
k_{10}	TBW	3.50	0.69-6.31	40.7
k_{10}	HSD	0.83	0.30-1.36	32.3

ECV=extracellular fluid volume; ICV=intracellular fluid volume, TBW=total body water volume (ECV+ICV); tv=typical value for the group; CI=confidence interval; CV=between-patient coefficient of variation; HSD=7.5% saline in dextran

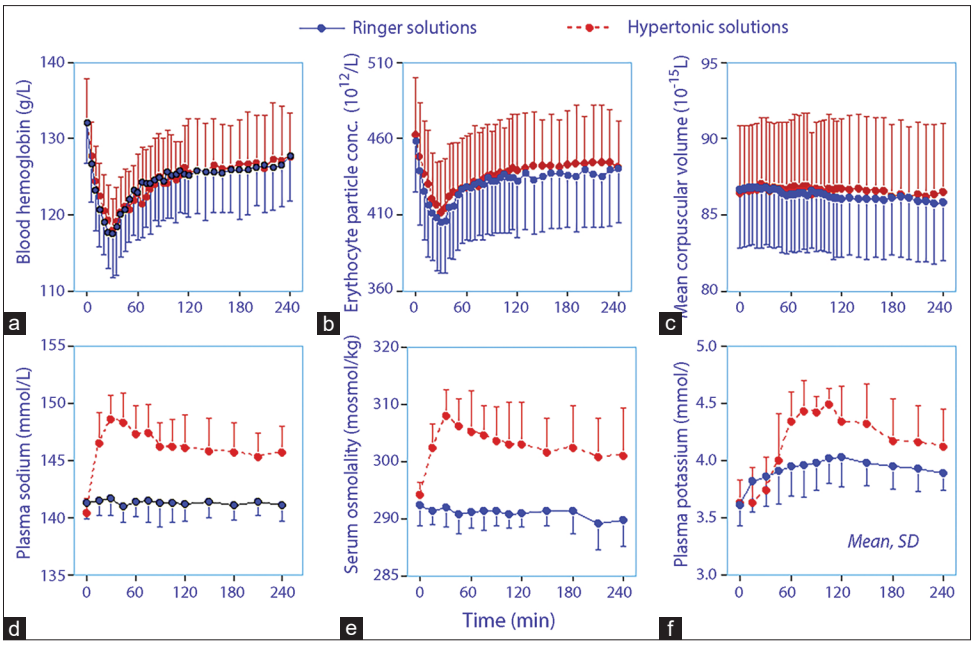

Figure 1: Basic blood chemistry. Data collected during and after infusion of 25 mL/kg of acetated or lactated Ringer´s solution (N = 30) and 3 or 5 mL/kg of fluid containing 7.5% saline (N = 20). (a, b, c): Indices of the erythron, (d, e, f): Plasma electrolytes

where U is the measured urine volume, Hb_o is the Hb concentration at baseline, and Hb is the concentration at a later time.

The data for each type of fluid were entered into the Phoenix software for nonlinear mixed effects, Version 1.3 (NLME, Pharsight, St. Louis, MO, USA) and analyzed on a single occasion for each type of fluid. The search routine used was the First-Order Conditional Estimation Extended Least Squares (FOCE ELS), which is slow but yields precise estimates of the unknown parameters (V_c, k_{12}, k_{21}, k_{10}, and k_b) in the model.[10]

Covariates were then added in sequence. The ICV, ECV, Hb_o, and body weight were evaluated as potential covariates according to *power models*. The uses of HS/HSD or Ringer's acetate/lactate were evaluated as *exponential models*. A covariate was accepted, and its addition to the model decreased the −2 log likelihood by >3.8 ($P < 0.05$) and the 95% confidence interval (CI) for the estimate did not include 0.

Statistics

Data are presented as the mean and standard deviation (*SD*), and comparisons between the groups were made by one-way analysis of variance followed by the Scheffé's *post hoc* test. Kinetic parameters were reported as the best estimate and the 95% CI. $P < 0.05$ was considered statistically significant.

Table 3: Population volume kinetic parameters in the final models for nearly isotonic and hypertonic crystalloid fluid

	Covariate	Best estimate	2.5% CI	CV%
Isotonic fluid				
tvV_c (mL)		4,732	4,165-5,299	6.1
tvk_{12} (10^{-3} min^{-1})		31.9	23.9-39.8	12.7
tvk_{21} (10^{-3} min^{-1})		25.2	18.6-31.8	13.3
tvk_{10} (10^{-3} min^{-1})		12.4	9.6-15.2	11.4
tvk_b (10^{-3} min^{-1})		5.6	3.0-8.3	23.5
Covariate effects				
k_{12}	ICV	−1.5	−2.5−−0.6	−31.2
k_{12}	Hb_o	−6.5	−8.6−−4.4	−16.7
Hypertonic fluid				
tvV_c (mL)		5,523	4,959-6,088	5.2
tvk_{12} (10^{-3} min^{-1})		29.5	21.2-37.8	14.2
tvk_{21} (10^{-3} min^{-1})		33.8	25.9-41.6	11.8
tvk_{10} (10^{-3} min^{-1})		6.2	5.0-7.5	10.1
tvk_b (10^{-3} min^{-1})		6.6	4.4-8.9	17.3
Covariate effects				
V_c	ECV	1.36	0.89-1.83	17.6
k_{10}	ECV	4.40	2.72-6.07	19.4
k_{12}	HSD	−0.70	−1.01−−0.39	−22.4
k_b	HSD	−1.47	−1.90−−1.03	−15.1

tv=typical value for the group; CI=confidence interval; ICV=intracellular fluid volume; ECV=extracellular fluid volume, CV=between-patient coefficient of variation; Hb_o=blood Hb concentration at baseline; mean 20.1 L; HSD=hypertonic saline dextran. Mean ICV is 18.8 L and mean Hb_o is 135 g/L

Results

The study comprised 50 intravenous infusion experiments in 20 healthy volunteers aged 32 (8) years [mean (*SD*)], had

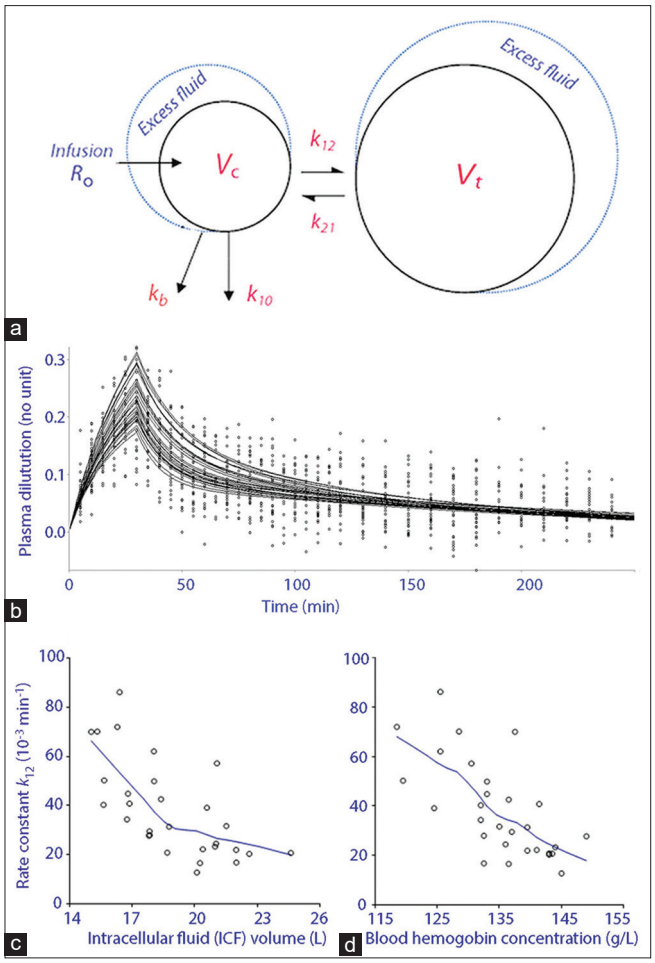

Figure 2: Kinetics of Ringer's solution (a) Schematic drawing of the volume kinetic model (b) Curve fit for the 30 infusions of acetated or lactated Ringer's solution (c, d) Covariates. The distribution rate constant k_{12} correlated inversely to the size of the intracellular fluid volume (ICV), and also with the baseline blood hemoglobin (Hb) concentration

heights of 180 (4) cm, and body weights of 80 (9) kg. Thirty infusions consisted or lactated or acetated Ringer's solution, 10 infusions of 7.5% saline, and 10 infusions of 6% dextran 70 in 7.5% saline (the latter two are called "hypertonic fluids"). All solutions were infused over 30 minutes, and the follow-up lasted 4 hours.

Basic biochemical data collected during the experiments are shown in Table 1 and Figure 1. The urine output in response to hypertonic fluid was three times the infused volume, whereas 40% of the infused Ringer's solution remained in the body after 4 hours.

The measured body fluid volumes are summarized in Table 2, top.

Sodium and osmolality kinetics

The kinetic analyses of the infused sodium and osmotic loads were based on 204 data points collected during the experiments with hypertonic fluid. The final parameter estimates are given in Table 2, bottom.

The volumes of distribution (V_c) for sodium and osmolality were 35% larger than for the ECV space as measured by bioimpedance. This "sodium space" increased to a greater extent with the measured TBW than with the body weight. The addition of dextran to the 7.5% saline accelerated the solute excretion, which might reflect better renal perfusion.

Ringer's kinetics

The kinetic model shown in Figure 2a was simultaneously fitted to 947 measurements of plasma dilution and 53 measurements of urinary excretion. The final curve fit is shown in Figure 2b and the parameters in Table 3, top. A large ICV decreased the rate constant that governs the rate of distribution of infused fluid from the plasma (V_c) to the extravascular space (i.e., k_{12}) [Figure 2c]. Second, the rate of distribution was reduced by a high Hb_o [Figure 2d]. No differences were found between lactated and acetated Ringer.

Hypertonic fluids

The initial curve fitting was based on the assumption that osmotically recruited water was allocated to the extravascular space (V_t). However, setting both the infusion and the translocation to the plasma space (V_c) resulted in superior curve fits (model without covariates −2 log likelihood −2,580 vs. −2,400).

The curve fit for the two hypertonic fluids is shown in Figure 3a, the covariates in Figures 3b-e, and the optimal parameter estimates in Table 3, bottom.

Simulations

Computer simulations were performed using the volume kinetic parameters on the Ringer's solutions and 7.5% saline [Figure 4]. A large ICV reduced the extravascular volume expansion following the infusion of Ringer's solution. A high ECV greatly increased the urinary excretion in response to 7.5% saline, which indirectly reduced the volume expansion of the plasma and the extravascular space.

Discussion

Body fluid volumes

The answer to the *primary hypothesis* is that a large ICV increased the plasma volume expansion during infusion of nearly isotonic crystalloid fluid, whereas a large ECV reduced the plasma volume expansion during infusion of hypertonic fluid.

These findings confirm that the size of the body fluid volumes influences the distribution and excretion of infused resuscitation

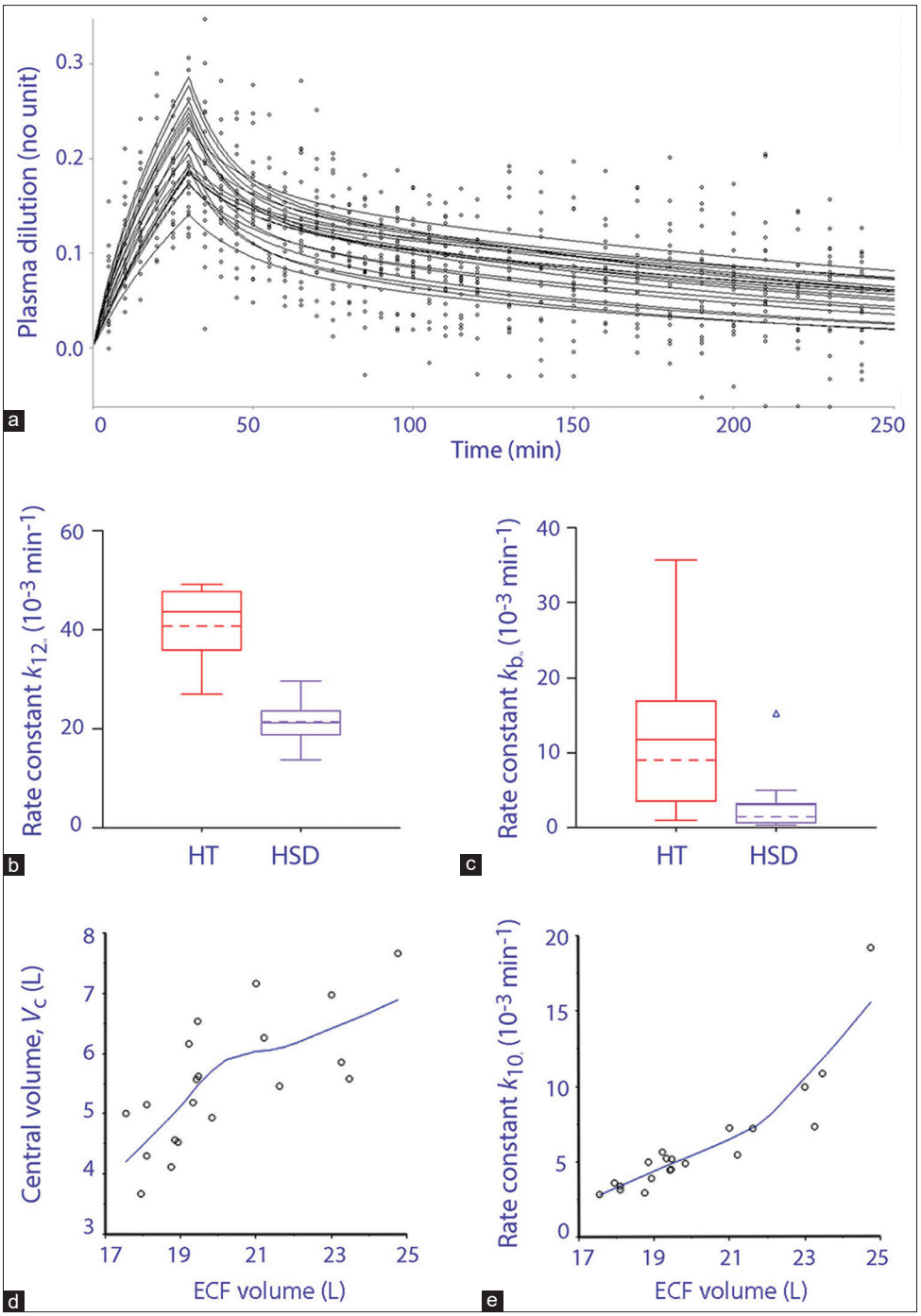

Figure 3: Kinetics of hypertonic fluid (a) Curve fit for infusions of 5 mL/kg of 7.5% saline (HS) and 3 mL/kg of 7.5% saline in 6% dextran 70 (HSD) over 30 minutes. (b, c) Parameters to which the choice of 7.5% hypertonic saline served as covariate. (d, e) Parameters to which the extracellular fluid volume (ECV) served as covariate

fluid. These data are relevant not only because the ECV and ICV change during the human lifetime but also because they seem to depend on the habitual intake of liquid.[4]

The details of the volume kinetic analysis offer a more mechanistic view of how these differences might occur. They show that Ringer's solution distributed more slowly from the plasma to the extravascular space when the ICV was large. The reason might be that a large ICV compresses the interstitial meshwork, thereby promoting a relatively greater rise in hydrostatic pressure on volume expansion. Moreover, the hypertonic fluids were excreted markedly faster if the ECV was large [Figure 4].

Hypertonic saline

Hypertonic saline in a 75% concentration with and without dextran added has been used for 40 years in ambulances,

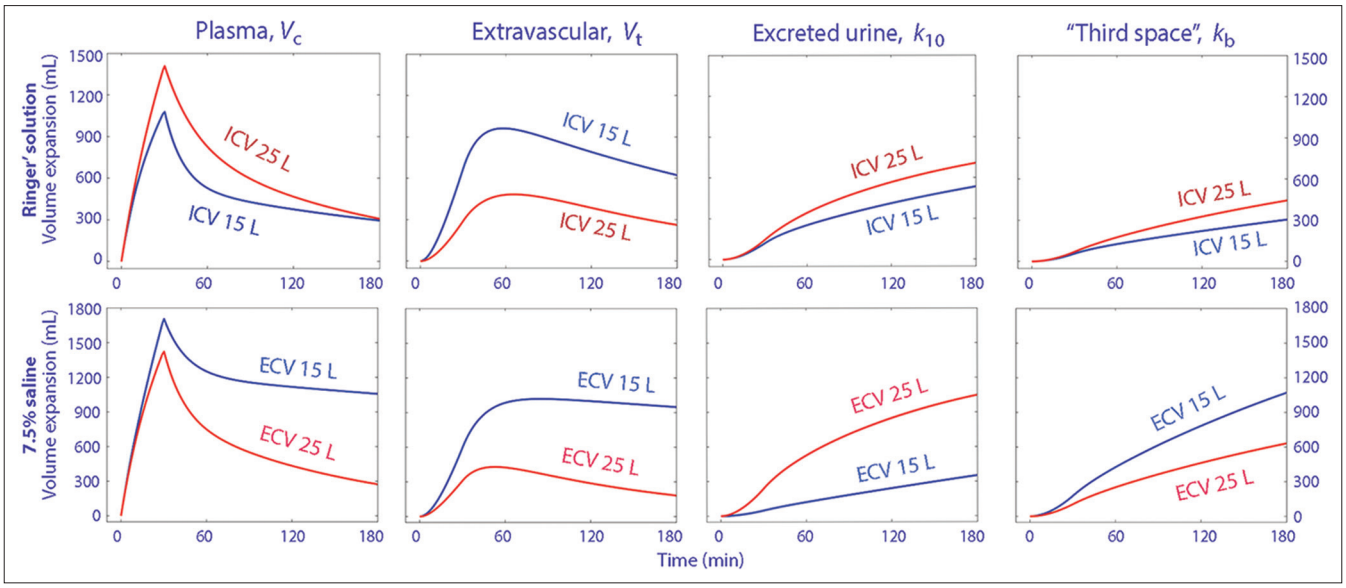

Figure 4: Volume expansion. Computer simulations of the expansion of the body fluid spaces on infusion of 25 mL/kg (= 2 L) of lactated or acetated Ringer´s solution (top row) and 7.5 saline (bottom row) over 30 minutes is infused depending on the size of the intracellular fluid volume (ICV) and extracellular fluid volume (ECV) *before* the infusions were initiated. Data were derived from Table 3. The administered saline was set to match the Ringer's volume when considering the osmotically recruited volume, the latter being 4.9 times the infused volume: 2 L/5.9 = 340 mL of 7.5% saline

rescue helicopters, and other emergency settings.[6,7] Infusion of 2 L of Ringer's solution and 400 mL of 7.5% saline created almost identical plasma dilution–time profiles [Figure 1a]. Osmotic recruitment of water from the erythrocytes with hypertonic saline seemed to be very small or absent, which is a surprising finding that has also challenged researchers in the past.[13] The site of osmotic withdrawal of fluid, if not from the erythrocytes, has previously been assumed to be the extravascular fluid compartment.[8] However, the curve fitting was superior when osmotic absorption of water was modeled to occur directly to the plasma, possibly by recruitment from the endothelium and cells adjacent to the bloodstream. The kinetic results presented here are based on that view.

The infused surplus of sodium ions with 7.5% saline was distributed quickly over a large fluid space that correlated significantly with TBW (*secondary hypothesis*). However, the "sodium space" averaged 67% of the body weight, while the bioimpedance showed that that TBW corresponded to only 49% of the body weight [Table 2]. The expansion of the sodium space beyond the measured TBW might be due to the deposition of excess sodium in nonosmotic form, as described by Olde Engberink *et al*.[14] By contrast, previous work shows that volume kinetic analysis based on diluting the plasma sodium with isotonic mannitol indicates 20% of the body weight, which corresponds closely with the ECV measured by bromide and iohexol.[11]

The volume of distribution was somewhat larger for the added osmolality than for the excess sodium, which might reflect that most plasma proteins have a negative charge (the Donnan effect) and bind some sodium in the blood. Serum potassium was increased more by infusion of 7.5% saline than by the Ringer's solutions, even though saline lacks potassium [Figure 1f]. The likely explanation is a translocation of potassium from the ICV to the ECV due to the acidifying effect of saline.[15]

Volume kinetics

The volume kinetic approach used here is an adaptation of conventional pharmacokinetics for infusion fluids.[7] The analysis detects a functional "wall" between the volume in which the fluid is infused (the plasma) and a more remote fluid space, called V_t. The model uses the same fixed parameters as in a two-compartment model with microconstants, except for an additional elimination rate parameter, k_b, which should be included if statistically significant.[12] This parameter represents what is called the "third spacing" in older literature and refers to the fluid that escapes to a remote compartment and is separated from the kinetic system.[16,17] With both types of fluid, k_b eliminated half as much fluid as was eliminated by urinary excretion. Whichever the precise mechanism "third spacing" is apt to reduce the plasma volume expansion in response to infusion fluid.

When the fixed parameters have been determined, a search is then made for individual-specific covariates that can modify the fixed parameter value in a subject.[10] For example, the distribution was slowed down if the Hb level was high [Figure 2d]. The important covariate for 7.5% saline was that a large ECV increased k_{10}, which governed urinary excretion. The addition of dextran to the 7.5% saline reduced

the rate of distribution by half, so the plasma volume expansion would be maintained longer [Figure 3b, no simulation shown].

The sodium and osmolality kinetics did not have a distribution function and were therefore evaluated as one-volume models. All infused sodium distributed in a single well-stirred volume, which means that equilibration between the circulating plasma, the cellular water, and the glycocalyx is more or less instantaneous. By contrast, the distribution of fluid volume between the plasma and extravascular space requires 30 minutes for completion, as shown in Figure 4.[16,18]

Limitations

The presentation involves four different infusion fluids. Lactated and acetated Ringer's are presented together, as no statistically significant differences were found between their population parameter estimates. The two hypertonic fluids were evaluated as one fluid but using covariance analysis to disclose the main difference between them, which was that 7.5% saline with dextran distributed only half as quickly as the plain saline solution.

The bioimpedance software has been calibrated with isotope dilution techniques,[19,20] but the ICV: ECV ratio obtained with bioimpedance is more – typically 1.5:1[20-23] than the 2:1 ratio that is reported in medical textbooks.[1,2] However, new measurements suggest that the 2:1 ratio corresponds to a situation when the habitual intake of water is low, whereas the ICV: ECV ratio is 1.5:1 or even 1:1 in subjects with a normal or high intake of fluid.[4]

The crude ECV and ICV were used in the evaluation, without correction for body weight, because the amount of infused fluid was varied according to the body weight. Moreover, rate constants are independent of infused fluid volume.

The present report is a secondary publication to two previously published studies, albeit with a different focus.[8,9]

The size of V_c was larger than usually found in volunteers. This means that the measured plasma dilution was somewhat smaller than expected in relation to the modeled expansion of V_c. In kinetic terms, the analysis places the functional "wall" separating V_c from V_t slightly outside the physiological plasma volume.

Conclusion

In healthy male volunteers, a large ICV retarded the distribution of Ringer's solution, whereas a large ECV accelerated the excretion of 7.5% saline with and without added dextran. These results suggest that the kinetics of infusion fluids partially depends on dietary habits and not only on gender, body weight, and age.

Acknowledgements

The author is grateful to the coauthor, Dr. Dan Drobin, of two original manuscripts, on which the present work is based. Dr. Drobin has approved recalculation of the data.

Data availability statement

The following Excel files are available as Supporting information.

S1 Krist data.xls The original data used for the kinetic analyses of crystalloid fluid

S2 HSoHSD data.xls The original data used for the kinetic analyses of hypertonic fluid

S3 Osmolalitet.xls The original data used to analyze the kinetics of sodium and osmolality

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Nil.

Conflicts of interest

The author holds a research grant from Grifols for studies of 20% albumin.

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