

Dan Drobin: Volume Kinetic Development and Application

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Volume Kinetic Development and Application

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LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to in the text by their roman numerals.

- I. Drobin D, Hahn RG:** 1996. Time course of increased haemodilution in hypotension induced by extradural anaesthesia. *British Journal of Anaesthesia* 77:223-226.

- II. Hahn RG, Drobin D, Stähle L:** 1997. Volume kinetics of Ringer's solution in hypovolemic volunteers. *British Journal of Anaesthesia* 78:144-148.

- III. Hahn RG, Drobin D:** 1998. Urinary excretion as an input variable in volume kinetic analysis of Ringer's solution. *British Journal of Anaesthesia* 80:183-188.

- IV. Drobin D, Hahn RG:** 1999. Volume kinetics of Ringer's solution in hypovolemic volunteers. *Anesthesiology* 90:81-91.

- V. Drobin D, Hahn RG:** Efficiency of isotonic and hypertonic crystalloid solutions in volunteers.

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ABSTRACT

Volume Kinetic Development and Application

Background: Fluid therapy is a cornerstone in shock resuscitation in a such as treatment of anesthesia induce down regulation of the circulation and also restores many different types of dehydrated states. Current guidelines for fluid therapy are, however, based on experience, rules of thumb and effect-related end points, such as restoration of physiological parameters, which do not directly represent the *volume effect* of the fluid. Many efforts have been made to measure the actual volume effect of different fluids. The methods used are mainly based on isotope labeling of substances. Such a method has two inherent limitations. One is that labeling of substances results in volume estimations from the dispersal of the substance in the body, often leading to the conclusion that the volume effect of the fluid acts in the same space. The second limitation is the use of backward extrapolation to estimate the volume that the tracer substance that was dispersed in at time zero, leading to a single estimation for each labeled substance infused. Such a method is not suited for *dynamic* analysis of fluid volume dispersal and elimination, whereas volume kinetics provides a time resolution.

Methods: This thesis is based on the analysis of serial measurements of blood hemoglobin concentration in conjunction with intravenous fluid infusion. In paper I, the dilution-time profile was used to calculate the relative intravascular percentage of the infused amount of volume. In papers II-V, the analysis was based on volume kinetics using four different models. In paper II, the VOFS1 and VOFS2 models were used; in paper III, the same models were used, but they were extended by a function that calculated the elimination rate parameter from the obtained urine volume to decrease the intercorrelation between parameters, VOFS2_{ur}. These models were used in paper IV and, in paper V, they were extended by a new peripheral space for the purpose of handling fluid recruitment from the most remote body fluid space governed by an infusion of hypertonic fluid and also an analysis based on

noncompartmental modeling. The development of this model also included a rate parameter describing the return of fluid the most remote body fluid space.

Results: Paper I showed that hypotension might modulate the preference of fluid to remain in the intravascular compartment. Papers II-V showed similar volume kinetic parameter results when no bleeding was induced and that the obtained volumes were significantly smaller than the expected extracellular spaces. Paper IV showed that hemorrhage resulted in a clearly reduced rate of elimination and that the V_1 reduced by about the hemorrhaged volume. The use of urine volume as an input measurement in the two-volume model was justified when there was a high degree of intercorrelation between the elimination rate parameter and the parameter for the peripheral fluid space (paper III). Paper I showed that time-dilution profiles can be used to study mechanisms behind the disposition of fluid in the body. Hypotension caused centralization of the administered fluid, although the fluid is usually given to prevent hypotension. Paper II showed similar parameter results from experiments with different infusion times and volumes, which is a prerequisite for using the model in different situations. Paper III successfully dealt with the occurrence of experiments involving the VOFS2 model, in cases where the analysis failed to provide good parameter results by reducing the parameters to be estimated, thus making possible less correlation in the results. Paper IV provided a nomogram for volume-related resuscitation in hemorrhaged human volunteers. Paper V compared the efficiency of five different infusion fluids and showed that volume kinetics could be used to analyze of the mechanism behind altered fluid handling. The increase in the dilution effect of dextran was not a result of a reduced elimination slope, but rather an increase in the direct effect on dilution.

Conclusion: Time dilution profiles can be used to analyze the functional mechanisms controlling fluid distribution and elimination. The obtained parameters were the about same in experiments using different infusion volumes and rates. This is indicating that the model is valid. It is necessary that the parameter results do not differ when infusion is changed if simulations to illustrate other infusion rates and volumes than what was used in the experiment, are performed. When strong parameter intercorrelation occurs, it is justified to use the urine volume in the calculation to reduce the estimated parameters so as to enhance the precision in the remaining ones.

Additionally, serial analyze of blood dilution and volume kinetic interpretations were useful for creating a dynamic dosage scheme for hemorrhage in volunteers and also in the comparison between different fluids pinpointing the specific functional mechanisms causing differences in fluid handling. Thus, volume kinetics provides a new tool for the analysis of fluid dynamics. The method is suited primarily for research on fluid dynamics in comparative studies, and for learning purposes using simulations, and possibly also for computer-controlled fluid administration systems. Volume kinetics should also be used in the development of new fluids in the search for specific properties. Additionally, it should be used to correct the estimation of the pharmacokinetic parameters for substances, that influences the internal fluid spaces, like colloids, artificial blood and diuretics. Volume kinetics is also a tool for the analysis of the mechanisms of pathological fluid handling, such as in septicemia, anesthesia, or heart failure (comparative studies).

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ABBREVIATIONS

Cl	Clearance (<i>used in pharmacokinetics</i>)
i.v.	Intravenous
k_r	Elimination rate constant
k_t	Intercompartmental rate constant
L	Liter
mL	1/1000 Liter
MSQ	Mean squared error
NaCl	Normal saline solution, NaCl 0,9 %
PD	Pharmacodynamic
PK	Pharmacokinetic
SD	Standard deviation
SEM	Standard error of means
V or V1	Central fluid compartment, unstressed volume
V2	Peripheral fluid compartment, unstressed volume
V3	Remote fluid space, unstressed volume
v1	Expanded central fluid compartment, stressed volume
v2	Expanded peripheral fluid compartment, stressed volume
v3	Reduced remote fluid space, stressed volume
VOFS1	Volume of fluid space model with one compartment
VOFS2	Volume of fluid space model with two compartments
VOFS2 _{ur}	Volume of fluid space model with two compartments using calculated elimination rate parameter
X	Amount at time zero
x	Amount at time n

INTRODUCTION

History of fluid therapy

Fluids have been given intravenously for the management of fluid deficits, for over 100 years. Sidney Ringer 1883, discovered that calcium containing tap water was better than distilled water in resuscitation. The understanding of the circulatory system and the importance of maintaining the circulatory volume was realized long ago¹. Furthermore the desired elements and their approximate concentrations in fluid compositions for intravenous plasma substitution became known at an early stage. However, the more precise dynamics (i.e. the volumetric disposition and elimination) of i.v. fluids are still not fully understood. Thousands of papers covering fluid therapy, its benefits and detriments, and different guidelines for its administration have been published over the last few decades^{2-6, 26}. However, the search for the optimal composition of fluid has slumbered for a notable time. Recently, the search for the optimal composition has entered a new phase including both new suggestions on resuscitation fluid, aimed in the military of the USA⁷, and also the development of volume kinetics⁸.

In early medical approach to venous therapy was bloodletting, a therapy that later "reversed" and turned into intravenous fluid therapy. The understanding of the circulatory system as a system placing the heart in the central role, pumping blood into the arteries and returning the blood through the veins, was first properly described by William Harvey in 1638. Despite not having the physiological knowledge of today, the first known intravenous infusions surprisingly occurred in 1492. Blood was then given to the pope from three youngsters by a vein-to-vein anastomosis in a desperate attempt to save the dying pope. Both the patient and the three donors died. As early as 1667, the first known successful animal-to-animal transfusion was made. And in 1818, the first transfusion successfully carried out on a patient suffering from hemorrhage during childbirth was performed by Dr. James Blundell. In 1830, the gold-plated steel needle for i.v. use was invented. A

publication in *The Lancet*, in 1831, by O'Shaughnessy⁹ describes the need for administering salts and water to cholera victims, an idea that was put into practice by Thomas Latta soon thereafter. During the 1930s, Baxter and Abbot produced the first commercial saline solutions. In the 1950s, plastic i.v. tubing replaced rubber tubing and the tubing device was extended for the first time to central positioning in the 1960s, which certainly represented a breakthrough for estimations of the state of hydration and the need for volume support¹⁰. The i.v. technique introduced a new delicate problem: i.v. therapy related septicemia. In the 1970s, an outbreak in the USA of sepsis due to sterilization failure caused the death of 100 people. And later during the Korean war, fluid overload became a common and lethal side effect due to a lack of knowledge about how infusates disperse and are eliminated during trauma.

Background

Theoretical concepts concerning fluid therapy have not accelerated in proportion to most other medical sciences. The reason for this remains unclear. Some facts may reflect contributing aspects. There is a gap between those who are able to construct mathematical models i.e. engineers and mathematicians, and physicians who could use such methods. This gap might be responsible for this delay in the evolution of research. The internal body environment is concealed from most direct measuring methods. The body holds a large amount of fluid contained in different more or less defined compartments¹¹ (anatomical and functional). These compartments are under continuous feedback control, resulting in an oscillating continuum throughout life. Sometimes changes are triggered by pathologic events, but mostly just by the natural diurnal rhythm. The internal homeostasis moves between endpoints and is always "on the road", which makes the search for the baseline state difficult or even unjustified.

One explanation for why functional body spaces should be modeled is that there is no precise direct method to measure the internal milieu. One example of the difficulties inherent in direct methods is the problem of measuring the hydraulic pressure in the interstitial matrix¹². Different methods produce different results, depending on how the measuring process itself interacts with the environment. A common method is implantation of small catheters which will hopefully equilibrate with the environment without inflicting bias in the system. Even if this is accomplished, the results reflect

only the pressure in a selected area and organ and recordings result in a mean over a certain period of time. Instruments do indeed affect the measurements. Therefore, it is justified to model systems, which represents another perspective, even though modeling has got other sources of error.

Elimination

Processes in nature occur surprisingly often in a fractal way. This can be observed in a variety of processes. Unstable atoms fall apart in a precise way. Within a defined time-interval 50% of the atoms are degraded and, in the next interval, another 50% (of the remaining number), are degraded. This is valid regardless of the number of atoms at the beginning. Trees have one stem, which divides into two branches, which in turn are divided into four branches, and so forth. The circulatory and respiratory systems divide and spread in a similar way. Certain shells grow in polynomial fashion, with the original shell formation becoming the center when it grows, and new shell-house protuberances grow larger directly on the previous ones and each new wing is nicely proportional to the previous one, forming a helix. When an apple is released from its twig, the speed it develops increases proportionally, depending on gravity, until it comes to halt on soil. The battery in your car is uncharged in an exponentially decaying manner, if no supply current is connected. The foundation for this can be attributed to a *scaling* phenomenon, since the next event scales to the preceding one (not to be confused with pharmacokinetic/pharmacodynamic scaling between animals).

The use of mathematical models has been widely adopted¹³ in parallel with the development of computers¹⁴. Models are now indispensable, for example, in simulations in situations where learning becomes more effective by allowing the user to stress the learning situation beyond what is reasonable in reality. Stressing systems may also reveal unexpected outcomes resulting in new knowledge. Modeling is performed in very early phases of drug development, both in the design of drugs in the search for useful dynamics, and also for subsequent dose recommendations. The use of modeling here is absolutely unquestioned. However, no corresponding mathematics had been applied to fluids until the development of volume kinetics (first abstract on volume kinetics applied on humans was in 1995, based on data from paper II).

Models for medical purposes are commonly used especially in the discipline of pharmacology/toxicology. Modeling of whole body fluid dynamics has some advantages over above described invasive ones; models describe the system *functionally*. A system consist of several *interdependent units*. Elimination frequently scales to what amount is present in a system, which applies to the elimination of drugs¹⁵ and fluid volumes.

Modeling

Models can be divided into compartmental¹⁶ or non-compartmental^{17, 96} (distribution free) models. Sometimes, non-compartmental modeling is misstated to be model-independent because of the lack of compartment and rate concepts. But, of course such models do reflect about the preferable manner in which the data should be described. The present work, is however, based on the compartmental analysis. The aim of volume kinetic modeling is to obtain knowledge concerning how infusates are being distributed and eliminated in the body and to acquire knowledge concerning the underlying functional components^{18, 20} (body spaces and fluid rates) that interfere with fluid handling.

Structural models that rely on wrong assumptions might provide the user with good predictions for fluid handling. Then the model acts like a "black box function". A structurally correct model might provide poor estimates for different reasons and reasonable results does not prove validity of a model. One must keep in mind that models in general are significant simplifications of reality²¹. Models can not take into account all functional and physiological courses of events. Models should be as simple as possible, since every function that is added to the model adds an assumption. Three main reasons for modeling can be distinguished²²⁻²⁴: (1) to converge profuse amounts of data into a few *numerical statements* (characteristics or "labeling") expressed as defined parameters. Modeling thereby *describes* fluid handling in a perspicuous way. (2) The model output can be used to *predict*. Good prediction is necessary in goal-oriented and individualized treatment. (3) The use and testing of models increases the understanding of the underlying system (heuristic application^{25, 97}).

A model, is in fact, a theory (assumption) of reality, based on *observations* and *experience*. A model structure is a mechanistic explanation of the processes behind courses of events. Scientific evolution begins with observations that subsequently lead to theories, which in turn can be tested experimentally and result in answers regarding the level of agreement between the hypothesis and reality. A multitude of theories can be woven into a generalized theoretical system that can be defined as a model. Results of hypothesis testing represents new observational data from which new theories, including in extreme cases, a paradigmatic shift, can evolve.

Answers are thus not the only form of progressive results. Instead new questions usually arise, which can develop into fundamental concepts in new theories (described by new models). This capability for revolutionary progress in scientific work is extraordinary and is the opposite to the rationalistic point of view (see below). Modeling can be a superb tool for exploring reality and to serve as an instrument for creating better future explanations which would not have been developed if the scientific search process by modeling had never been initiated.

This hypothetical-deductive empiricism, which emphasizes the role of experience in human knowledge and minimizes the role of reason, constitutes the foundation of scientific progress. This represents the prerequisite for science as described by Hippocrates: the empirical, hypothetical-deductive method of understanding, as opposed to the philosophical rationalism, in which the universal and necessary principals are self-evidently understood without observations, and their consequences being deduced. Pure reason would then correct distortions. Here, testing of the hypothesis can only result in either the theory is accepted as true or that new auxiliary-theories have to be produced in order to explain why testing resulted in a deviation from the implicit “knowledge”, retrospectively confirming the original theory. Such a system can never be questioned in terms of its own structural view. When modeling, statements inherent in a model are tested by the facts to which they refer.

Volume kinetics

The volume kinetic model in its most simple form, the VOFS1 model, is explained here:

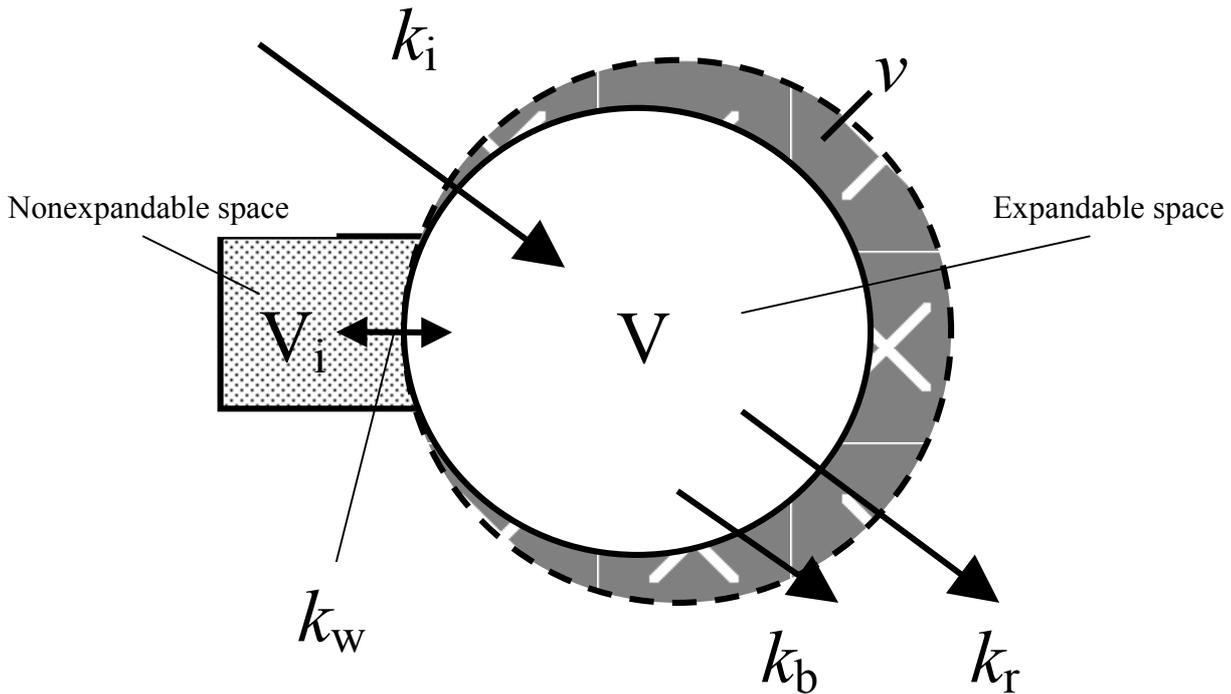


Fig 1. The one volume fluid space model, VOFS1.

A body fluid space V , (unstressed volume) is present when the system contains no excess fluid. An i.v. infusion is given at a constant rate (k_i), into the central body fluid compartment (V). This expands the unstressed volume (V), producing a stressed volume (v). By spontaneous diuresis and evaporation, fluid leaves the body fluid space (V), at a linear rate (k_b). The nonexpandable space (V_i) is accessible for exchange of water molecules, described by a rate constant (k_w). If k_w in each period of time promotes the same flux of molecules in both directions (only exchange) no net flux of volume enters V_i and V_i is consequently not expanded, even though deuterium

would indicate this space. If, on the other hand, k_w did promote a net flux of volume between spaces, the result would be a volume effect in V_i . Since volume kinetics describes net volume effects the k_w and V_i is not included in the concept. The dilution dependent elimination (k_r), is governed only by excess fluid or overflow volume, in the system. Overflow volume is the difference between v and V ; $(v-V)$. The amount of overflow volume to the unstressed volume V , constitutes the force vector for fluid elimination, $(v-V)/V$, and is measured as the dilution in the system (see below). This model, simple enough, creates a need for exponential calculation because elimination scales to the ratio of excess fluid to the unstressed volume that the system is striving at. The elimination equation becomes:

$$\text{Elimination rate (mL/min)} = k_r \text{ (mL/min)} * (v-V)/V \text{ (no sort)}$$

The important assumption for easy mathematical analyze is that the scaling factor remains the same during a determined time interval. This means that in the time t , for example 50% of substance or volume is lost from elimination. The same ratio (and thus not amount) is lost during the next time interval, and so forth. At infinity time, an infinitely small amount will theoretically still be there, and zero is never obtained. Assuming that X is the amount at time zero, that one interval for a 50% reduction is t , n is the number of reduction intervals and x is the amount at time $n * t$, (t is one interval and can be excluded). This can be mathematically expressed as:

$$x = X * 0.5^n$$

It is more convenient to use the base in the natural logarithm system. The relation for a value a , to the natural base is:

$$a = e^{\ln a}$$

Using $a = 0.5$, and including n , the function becomes:

$$x = X e^{\ln 0.5 n}$$

This represents the formula that is the fundament in pharmacokinetics. It describes the curve slope from elimination when a substance is proportionally eliminated. The point attractor is x , and X is the baseline value. The same formula is used in volume kinetics, however, since volume kinetics uses an endogenous point attractor as blood hemoglobin or plasma albumin, a conversion is applied, to deduce the relationship between the dilution that is used in the model as the factor that governs elimination, and the way dilution is measured. If X is an endogenous substance in the plasma at time zero, and x is the same substance at any time point we get the following deduction:

$$\left| \frac{X-x}{x} \right| = \frac{\left(\frac{X_{tot}}{V} - \frac{X_{tot}}{v} \right)}{\frac{X_{tot}}{v}} = \frac{v}{X_{tot}} \times \left(\frac{X_{tot}}{V} - \frac{X_{tot}}{v} \right) =$$
$$\frac{vX_{tot}}{X_{tot}V} - \frac{vX_{tot}}{X_{tot}v} = \frac{v}{V} - \frac{v}{v} = \frac{vV}{Vv} - \frac{vV}{Vv} = \frac{v-V}{V}$$

By measuring an endogenous substance (x) it is possible to transform the result to a dilution $[(v-V)/V]$ that is used in the volume kinetic model that describes the elimination:

$$\text{Elimination rate} = k_r * (v-V)/V$$

OBJECTIVES

The novel approach of using time-dilution profiles in the analysis of fluid dynamics was tested, evaluated, and developed for the purpose of validating this approach, in order to enhance its precision, and to use the concept for guidance in clinically related situations.

I specifically concentrated on the following questions:

1. Can the time-dilution profile provide information on the dynamics of infused fluids?
2. Does volume kinetics produce stable results with different infusion strategies and do the results correspond to what is expected?
3. Could better results be obtained by introducing information about one parameter to reduce the parameters in the estimating process?
4. What specific functional mechanism controls fluid dynamics in the hemorrhagic state, and what would a fluid resuscitation recommendation look like after different stages of hemorrhage?
5. Different fluids have different dynamics. What functional mechanism is responsible for their disposition and elimination? How do fluids of different compositions correspond to each other.

ETHICAL CONSIDERATIONS

All experiments were approved by the local Ethical Committee and the participants gave their written informed consent prior to the studies.

Patients

Patients participated in paper I, in which they were given i.v. fluid at a low rate during 50 minutes. They were scheduled for a urological operation and for regional anesthesia in accordance with the hospital routine. No adverse events were seen. Surgery followed as scheduled after the experiments were ended.

Volunteers

Volunteers participated in papers II-V. Females participated in paper II, males in the remaining papers. The infusion rates were moderate to high, the highest infusion rate being the 25 mL/kg over 15 minutes used in paper II. Several volunteers reported feeling an abdominal lump and also a paresthetic sensation around the mouth during the highest infusion rate. Apparently the rate was too high and was not used further. However, no volunteer discontinued the experiment, since the sensations were mild to moderate and occurred only during the end of the most rapid infusion and stopping the infusion caused the sensations to disappear. No side effects were seen in paper III, and in paper VI, a blood loss of 900 mL in the recumbent position caused nausea and low blood pressure in two cases which was treated successfully with ephedrine. In paper V, one subject terminated the study because of headache and another because of pain in the arm. Both received 7.5% saline. Three other volunteers reported mild to moderate pain in the infusion arm.

MATERIALS and METHODS

Subjects

In paper I, 22 elderly men, ASA I-II, mean age 71 (range 38-85), scheduled for a urological surgery under extradural anesthesia were studied. In paper II, six female volunteers, mean age 32 (range 23-46), in paper III, 15 male volunteers, mean age 35 (range 24-42), in paper IV, 10 male volunteers, mean age 28 (range 23-33) and finally in paper V 10 healthy male volunteers, mean age 32 (range 24-44), were studied.

Fluids

Ringer's acetate (Pharmacia, Uppsala, Sweden, ionic content in mmol Liter⁻¹: Na⁺ 130, K⁺ 4, Ca²⁺ 2, Mg¹⁺ 1, and Cl⁻ 110, and acetate 30) were used in papers I-V. In paper V, Ringer's lactate, 7.5% saline, and 7.5% saline in 6% dextran was used. The hypertonic fluids were both prepared by the local pharmacy. All fluids were at the ambient room temperature when infused.

Procedure

All experiments started in the morning between 8 and 10 a.m. (papers I-V). The body weights of the patients, were obtained from the surgical ward records, whereas the volunteers were weighted in the morning before the experiments began. The subjects fasted over night in paper I and III, as recommended, before anesthetic and surgical intervention. The volunteers in papers II and IV had a light meal consisting of one glass of milk or water to drink and one sandwich prior to the study intervention. The infusion was controlled and held at a constant rate by infusion pumps (IVAC 560, San Diego, CA, USA, papers I-II, and Flo-Gard 6201, Baxter Healthcare, Deerfield, IL, USA, papers III-V). In studies IV-V, bioimpedance¹⁹ measurements were taken before each session in order to detect differences in hydration prior to the i.v. load. The monitoring in paper I consisted of manually obtained blood pressure measurements and continuous ECG recordings. In paper III, the monitoring included arterial pressure, pulse oxymetry and ECG (HP 56S, Hewlett-Packard Co., MA, USA)

and, in papers IV-V, the same monitoring was carried out (Propaq 104, Protocol Systems Inc., Beaverton, Ore., USA).

The experimental procedure is quite the same throughout this thesis and is not difficult or mysterious. However, the necessary focus on the mathematical core structure of volume kinetics often raises questions about the experimental design for volume kinetics-related experiments. Questions like "Do you have new catheters somewhere in the body?" are not unusual. Therefore, a survey of the procedure is presented below. Basically, the procedure is simple in its framework, although it takes some effort to perform all steps in a proper and prudent way. Many steps are to be done sequentially with short time intervals. Any source of error along this course complicates the process to various degrees. The main steps are as follows:

1. Weighing of subject and insertion of two i.v. cannulas.
2. Resting for 20-30 minutes for body red cell equilibration.
3. Blood sampling for baseline notation.
4. Infusion and blood sampling during and after the infusion. Sequential infusions can be given.
5. Data collection and storing, the point attractor being the hemoglobin or albumin concentration.
6. Computer runs in MatLab, using nonlinear least square regression curve fit procedure, by a modified Gauss-Newton method, and one or several kinetic models.
7. Data overview and F test model selection.
8. Possibly new mathematical model development, followed by a return to level 1.
9. Model discrimination between new models and existing models.
10. Data output storing.
11. Eventual simulations based on parameter results.
12. Statistical analysis of parameter results or results (dilutions at predetermined time points) from simulated curves.
13. Result presentation.

An experiment is performed by infusing an i.v. solution during a predetermined time. Blood samples are taken during and after the infusion. In this thesis post infusion time has been included in the sampling session. This is not required, however. It is possible to follow the process during a continuous infusion, which is considered a steady-state situation. However, this would require large amounts of fluid that would probably alter handling by the body significantly, or if smaller volume is used, the resulting dilution could be too small and hidden in noise.

The time interval between samples should be about 5-10 minutes. Hemoglobin and occasionally, albumin concentrations are measured from these samples. From these concentrations, a curve showing the dilution of the chosen point attractor during the infusion and the restoration that occurs when the infusion is stopped is analyzed by a least-square regression method that results in a curve fit for the model to the data presenting the parameter results and their intercorrelations and standard deviations (papers III-V). In paper II, a random search method was used which randomly tests parameter values until the MSQ does not improve in 15 iterations. No covariance matrix was given by this method. In papers III-V, the method is based on matrix algebra, in which iterations are also used, but now the model adds corrections to the previous parameter values until the change in an iteration is less than 0.1% (can be adjusted to any value, but the method is very robust to changes in the improvement level). The corrections are based on the derivative of a gradient function.

One blood sample usually requires about 3 mL of blood in the laboratory at Söder Hospital, resulting in the total amount from one individual and one experiment, of about 110 mL or more. This limits the possibility of making additional analysis requiring more blood. Smaller amounts can be analyzed using vacutainers for children, but our laboratory does not handle these automatically, making large scale use more difficult. The first sample is taken routinely in duplicate. The first measurement serves as a baseline value, according to which the entire calculation is dependent, where X is the baseline value for the point attractor $[(X-x)/x = (v-V)/V$, *no correction for hematocrit made here*]. Unpublished data show that an arbitrary deviation in the baseline value may alter the results somewhat. The magnitude of this alteration is about one tenth of the input variance.

To prevent coagulation in the cannula, NaCl 0,9% is returned after every blood sample. NaCl contamination is withdrawn together with a few milliliters of blood in a syringe before the sample is taken. This is returned immediately after the sample has been taken. The amount of saline given and whether or not the subjects being fasted, determines the input setting of the constant for the linear rate of elimination, k_b . If blood pressure is recorded, it is preferable obtained directly after each blood sample, not to alter the hemoglobin concentration by obstructing the arm. The arm that is used for blood sampling is also used for pressure monitoring because otherwise blood pressure measurements would obstruct infusion. The infusion is never given in the same arm used for sampling. The circulatory monitoring should follow blood sampling to allow an equilibration time between stasis and sampling. The urine volume has been measured at this point after ending the session. The urine volume is used sometimes when the model output is imprecise, which relates to difficulties in estimating parameters with acceptable standard deviations, which may occur.

Hemoglobin concentration is the main point attractor in volume kinetics. In paper V, we have improved the precision by also determining the red blood cell count and the mean corpuscular red cell volume, subsequently used for the calculation. This has the advantage of reducing the errors caused by the analyzing equipment. However, this procedure does not reduce errors from the sampling itself, as the two measurements are taken from the same sample glass. As the hypertonic solutions might change the red cell volume differently from the hemoglobin concentration, the mean red cell volume was measured in paper V. The influence of using one (normally obtained) or two decimals of the red cell count has been evaluated and no significant difference was found.

MatLab is an extremely powerful computer program initially developed for professional use by engineers and in technical research. The programming has been developed to fit our demands in collaboration with expert help from Lennart Edsberg, (the Royal Institute of Technology), Stockholm, Sweden.

The results of development has been published stepwise and many side-track options have been examined. The volume kinetic development in this thesis include:

1. Basic conclusions about serial measurements of hemoglobin. Paper I
2. VOFS1 and VOFS2, no intercorrelation matrix. Paper II
3. Urine volume as an input variable, intercorrelation matrix. Paper III
4. The use of above models after hemorrhage. Paper IV
5. VOFS3 for experiments using hypertonic solutions. Paper V

Statistics

The statistics used in this thesis are the mean and standard deviation (papers I, II, V), or the mean and standard error of mean (SEM, papers II, VI). When a skewed distribution is present, the median and 25th-75th percentiles were used (papers III, V). The results were then analyzed by the paired *t* test (papers I, IV), and one-way analysis of variance (ANOVA, paper, I, IV, V), followed by the Dunnet test (paper IV), the Newman-Keul test (paper V), two-way ANOVA and repeated-measures ANOVA, followed by the Scheffé test and simple linear regression (paper II). Differences between methods were compared using the Wilcoxon matched-pair test or the Mann-Whitney *U* test, as appropriate (paper III). Correlations were evaluated by linear regression with *r* = correlation coefficient (paper III) or by multiple linear regression (paper I). Statistical significance was considered to occur at $P < 0.05$ (papers I-V).

APPENDIX

Volume kinetics

In the simplest volume kinetic model, the osmotic shift $f(t)=0$ and V_2 is not statistically significant by the F test.³ The volume change of the single expandable body fluid space is then indicated by the dilution of the venous plasma according to Equation 1:

$$\frac{dv}{dt} = k_i - k_b - k_r \frac{(v - V)}{V} \quad \text{[Equation 1]}$$

The existence of V_2 is said to be statistically justified if the lowest possible average difference between the model-predicted and measured data points (mean square error, MSQ) is significantly reduced by fitting the solution to Equation 2 to the measured data points instead of the solution to Equation 1. If the osmotic shift is still $f(t)=0$, the situation in the central body fluid space, V_1 , and the peripheral body fluid space, V_2 , are as follows:

$$\frac{dv_1}{dt} = k_i - k_b - k_r \frac{(v - V)}{V} - k_t \left[\frac{(v_1 - V_1)}{V_1} - \frac{(v_2 - V_2)}{V_2} \right] \quad \text{[Equation 2]}$$

$$\frac{dv_2}{dt} = k_t \left[\frac{(v_1 - V_1)}{V_1} - \frac{(v_2 - V_2)}{V_2} \right] \quad \text{[Equation 3]}$$

Solutions to these differential equations have been published in previous work.³

When hypertonic sodium is infused, $f(t)>0$, and water is translocated to v_2 from a remote body fluid space, v_3 , at a rate governed by the osmotic load (see “Osmotic fluid shift”, below). In case V_2 is not statistically justified by the F test, the following differential equations show the changes in the volume of v_1 and v_2 , respectively:

$$\frac{dv_1}{dt} = k_i - k_b - k_r \frac{v_1 - V_1}{V_1} + f(t) - k_{31} \frac{v_3 - V_3}{V_3} \quad [\text{Equation 4}]$$

$$\frac{dv_3}{dt} = k_{31} \frac{v_3 - V_3}{V_3} - f(t) \quad [\text{Equation 5}]$$

Introduce $w_1 = \frac{(v_1 - V_1)}{V_1}$, $w_2 = \frac{(v_3 - V_3)}{V_3}$ and we obtain:

$$\frac{dw_1}{dt} = \frac{k_i - k_b}{V_1} - \frac{k_r}{V_1} w_1 + \frac{1}{V_1} f(t) - \frac{k_{31}}{V_1} w_2$$

[Equations 6 and 7]

$$\frac{dw_3}{dt} = \frac{k_{31}}{V_3} w_2 - \frac{1}{V_3} f(t)$$

Introduce vector and matrix notation:

$$\bar{w} = \begin{pmatrix} w_1 \\ w_2 \end{pmatrix}, \quad A = \begin{pmatrix} -\frac{k_r}{V_1} & -\frac{k_{31}}{V_1} \\ 0 & \frac{k_{31}}{V_3} \end{pmatrix}, \quad \bar{a}(t) = \begin{pmatrix} \frac{k_i - k_b}{V_1} - \frac{f(t)}{V_1} \\ -\frac{f(t)}{V_3} \end{pmatrix} \quad [\text{Equation 8}]$$

The differential equations in Equation 8 can be written as:

$$\frac{d\bar{w}}{dt} = A\bar{w} + \bar{a}(t) \quad [\text{Equation 9}]$$

The solution of this linear system of differential equations is:

$$\bar{w}(t) = e^{At} \bar{w}(T) + \int_T^t e^{A(t-s)} \bar{a}(s) ds \quad [\text{Equation 10}]$$

where e^{At} is the exponential matrix, T is the initial time, and $\bar{w}(T)$ the corresponding initial value. The integral can be evaluated if $\bar{a}(t)$ is approximated by a constant \bar{a}_k in the time interval $[t_k, t_{k+1}]$. The numerical solution \bar{w}_{k+1} at $t = t_{k+1}$ is then computed recursively from

$$\bar{w}_{k+1} = e^{A\Delta t} \bar{w}_k + (e^{A\Delta t} - I) A^{-1} \bar{a}_k, \quad k = 0, 1, \dots, N-1 \quad [\text{Equation 11}]$$

where $\Delta t = t_{k+1} - t_k$, $\bar{w}_0 = \bar{w}(T)$.

The **3-volume model** is described by Equation 9 with

$$\bar{w} = \begin{pmatrix} w_1 \\ w_2 \\ w_3 \end{pmatrix}, \quad A = \begin{pmatrix} \frac{-k_r}{V_1} - \frac{k_t}{V_1} & \frac{k_t}{V_1} & 0 \\ \frac{k_t}{V_2} & -\frac{k_t}{V_2} & -\frac{k_{32}}{V_2} \\ 0 & 0 & \frac{k_{32}}{V_3} \end{pmatrix}, \quad \bar{a}(t) = \begin{pmatrix} \frac{k_i - k_b}{V_1} \\ \frac{f(t)}{V_2} \\ \frac{-f(t)}{V_3} \end{pmatrix} \quad [\text{Equation 12}]$$

The form of the solution is given by Equation 10, and after approximating $\bar{a}(t)$ with piecewise constant values as in the 2-volume model, the numerical solution is obtained from Equation 11.

Osmotic Fluid Shift

The osmotic shift of water, $f(t)$, which occurs when hypertonic fluid is infused i.v., was estimated with guidance from standard text books in physiology. An osmotic shift is known to occur across the cell membrane and exchanges water from the extracellular to the intracellular fluid space, which amounts to 20% and 40% of the body weight (BW), respectively.⁷ Using a baseline osmolality of 291 and a calculated osmolality of 2458 mosmol/kg for the hypertonic fluid, the translocated volume, which can only accumulate in expandable body fluid spaces of the kind identified by volume kinetics, can be obtained from the equation:

$$f(t) = \frac{BW * 0.2 * 291 + \text{added osmolality}}{BW * 0.2 + \text{translocated volume}} = \frac{BW * 0.4 * 291}{BW * 0.4 - \text{translocated volume}}$$

Hence, the first mL of infused 7.5% NaCl translocated 4.9 mL of water. The osmotic force became progressively reduced for each subsequent amount of infused fluid since the osmolality of all body fluids gradually increased. Therefore, $f(t)$ was entered as linear function in the analysis process where $f(t)$ at each point in time was governed by the total amount of infused fluid.

RESULTS

Blood dilution induced by an intravenous infusion evolved in a decaying manner during infusion and decreased rapidly during the first 30 minutes after the infusion and decreased more slowly over the remaining time (papers II-V). Blood dilution could be used as an indicator of intravascular volume changes (papers I-V). Both blood hemoglobin and albumin could be used as point attractors in the kinetic calculation (papers II-IV), and the measured urinary volumes corresponded to the model-estimated volumes (paper II-VI, Fig. 4 paper II) When the mathematical analysis of the obtained blood dilution curves is extended with the integration of time, the possibility of both compartmental (papers II-V) and noncompartmental modeling (paper V) emerges, allowing pin-pointing of different fluid handling mechanisms. In paper I, the dilution obtained by an intravenous infusion was correlated on the systolic blood pressure. There was also a time delay between the hypotension, which appeared before the increasing blood dilution, amounting to about 15 minutes in the hypotensive group. The spread of the analgesia in the hypotensive group, was wide (Th. 4.3) and the heart rate increased and remained elevated during the observation time. In the normotensive group, the spread of analgesia was less pronounced (Th. 7.1) and the heart rate also increased during the first 12 minutes, but then it suddenly decreased toward baseline (Fig.1. paper 1). The fluid retained toward the end of the observation time was 36% of the infused volume in the normotensive group and 50% in the hypotensive group. Two distinctly separated phases were observed in the hypotensive group: the decrease in arterial pressure and the decrease in hemoglobin concentration.

The stability and linearity, necessary for future kinetic simulations based on compartmental parameter results were confirmed in paper II (Table 1), based on experiments using different infusion volumes and rates. All data assembled for kinetic purposes (papers II-V) could be fitted to the VOFS1 model, and provided results with low intercorrelation and low standard deviations although the majority of the

experiments had an optimal fit to the VOFS2 model. In the female volunteer group (paper II), 1/3 of the cases showed a best fit according to the VOFS1 model and the corresponding figure in the male volunteer group was about 1/5 (papers III-V). VOFS1 significance was more likely to occur if urine production was prompt (papers II-V). Additionally, the VOFS2 summed volumes (V_1+V_2) were significantly larger than the volume V in VOFS1 when the VOFS2 model was appropriate. The parameter results for normovolemic male volunteers were similar (papers II-V), considering that the procedure evolved during the time and that the greatest differences were between male and female volunteers. Occasionally, experiments were F test selected for the VOFS2 model although this model failed to provide acceptable estimates (paper II). The reason for presenting some data according to the VOFS1 model against the F test suggestion was that the parameter estimates were highly intercorrelated ($r < -0.98$). This correlation always occurred between the secondary fluid space, V_2 , and the elimination rate parameter, k_r , and was associated with a large uncertainty in the obtained parameter estimate, producing a large standard deviation. In those cases where uncertainties in estimates were found, the use of measured urinary volumes for the calculation of k_r (concluded in paper III, used in paper IV-V) resulted in a marked improvement in the analysis. Applying this concept in the VOFS1 or VOFS2 model increased MSQ. The individual standard error of the single expanded body fluid space in VOFS1 increased and no cases analyzed in the VOFS1 model benefited from such use. Applying it to the VOFS2 model in general resulted in similar problems and tended to increase the V_2 out of proportion, i.e. rising from 10 L to more than the body volume. However, when a case was F test selected to the VOFS2 model which failed to produce parameter results with less intercorrelation than $r < -0.98$, the collected urine volume should preferably be used in the calculation of the elimination rate parameter, k_r . When both models (VOFS1 and VOFS2) agreed, V_2 approached 10 L (Fig. 4, paper III).

Hemorrhage increased the efficiency of the administered fluid in supporting plasma volume, which was an effect that correlated with a diminished urinary response, seen as a reduced k_r which was 107 during normovolemia (mL/min), 44 after a 450 ml hemorrhage, and 34 after a 900 ml hemorrhage. Hemorrhage reduced the central compartment by about the same amount as the shed plasma volume, thus reducing V_1 from 3.7 L in the normovolemic group to 3.5 after the 450 mL hemorrhage and to

3.0 after the 900 mL hemorrhage. Reductions of k_r and V_1 both act to increase the central volume effect of an infusion (Fig. 3, paper IV).

Hypotension elicited by regional anesthesia also correlated to an allocation of i.v. fluid to the intravascular compartment (paper I). Another important factor that alters the distribution of infused fluid in the body spaces and the efficiency of the fluid was the rate of infusion (paper II). The infusion volume of 25mL/kg given at 15, 30, 45, and 80 minutes resulted in differences of the administered fluid to dilute the plasma. The slowest rate was most effective and the highest rate was least effective (Fig. 2, paper II). Only the fastest rate induced mild symptoms such as a sense of feeling swollen, an abdominal lump, slight dyspnea, headache, and analgesia around the lips. When hypertonic solutions were administered, symptoms of headache (one subject terminated the study) and pain in the arm (also leading to termination of one session), and mild to moderate pain in the infusion arm reported by three other volunteers two of which developed thrombophlebitis. Thirst was consistently reported when hypertonic fluids were infused. The infusion volumes and rates required to reach a predetermined dilution (ratio of blood volume increase) and to maintain the achieved dilution are given in the nomogram for normovolemic and hemorrhaged males (450 mL and 900 mL (Fig. 5 paper IV).

The relative efficiency of different isotonic and hypertonic fluids in diluting the plasma was found in paper V using both a compartmental and a noncompartmental approach. The efficiency of a fluid to dilute the plasma was highly correlated with the tonicity of the fluid. Isotonic fluids did not differ significantly, but there was a tendency for normal saline to be a better plasma expander than both of the buffered Ringer's solutions. Hypertonic saline in dextran had almost twice the capacity to dilute, expressed as the area under the dilution curve, (84.8 L^{-1}) as did hypertonic saline (45.3 L^{-1}) when the obtained area under the curve was scaled to the infused volume. Isotonic solutions averaged only about 1/8 of the best solution (12.0 L^{-1}). Urine production was smaller when the dose was smaller, i.e. in the hypertonic groups, 685, and in the isotonic groups, 1000. When the sampled urine volume was divided by the dose administered, the median value were 51 for isotonic fluids 185 for 7.5% saline and 273 for 7.5% saline in dextran. The variation in dilution time curves during infusion when simulation was performed to reach a predetermined dilution of

20%, was very small. However, the subsequent period showed a larger variation between groups. This pattern was also recognized within groups. This simulation added some results regarding the differences between the solutions. To reach a 20% dilution, a factor was multiplied by the infusion volume. This factor was 0.87 for normal saline, 0.85 for Ringer's lactate, 0.92 for Ringer's acetate, 0.27 for hypertonic saline, and 0.16 for hypertonic saline in dextran. Using saline as a reference, the relative volume effect was 0.80 for Ringer's lactate, 0.77 for Ringer's acetate, 3.23 for hypertonic saline, and 6.05 for hypertonic saline in dextran. On comparing what a dose increase actually does to the dilution time curve, it became evident that a dose increase could be transformed into a "time gain", describing the time it takes when a dose is increased to give twice the dilution for the upper dilution curve to reach a dilution value on the lower curve. This concept is introduced to illustrate whether an increase in an infusion of a certain solution results in an extended effect, i.e. this effect is dependent on the small slope decay in the late elimination (Fig. 6, paper V). The time gain was about three times greater with isotonic fluids than with hypertonic ones. The addition of dextran did not noticeably alter the slope of elimination.

Serum sodium concentration increased by about 10 mmol/L after an infusion of hypertonic solution. A phenomenon seen during the volume kinetic curve fitting procedure, was that the curves dipped transiently under the regression curve at 30-45 minutes after ending the infusion (papers II-V). There were no differences in the volume status of the volunteers between the groups when entering each session (paper II, VI-V) as measured by the bioimpedance device.

DISCUSSION

Fluid resuscitation is fundamental in the medical management for maintaining the body fluid homeostasis in order to prevent circulatory failure in the hemorrhagic state and during the relative hypovolemia induced by anesthesia²⁷⁻³⁰. Autotransfusion is one component of hypotension and constitutes a fluid shift from extravascular spaces to the blood stream, thus increasing the circulating blood volume^{31,32}. Isotonic crystalloid solution constitutes the prevailing compound for intentional plasma volume support. However, colloid solutions have long been known to be more dose-efficient for volume support and are in rather frequent use in Scandinavia, but not in the USA. Recently, the hypertonic solutions (7.5% sodium chloride), that have long been recognized in possessing almost magic effects in restoring the compromised hemorrhaged circulation^{33, 34}, have been recommended by the US army⁷, and have also been licensed with the addition of 6% dextran in Scandinavia and are recommended by the Swedish army. Plasma substitutes for i.v. administration differ tremendously in composition. The hypertonic saline has about 8 times the sodium concentration of that of normal saline. Many colloid variants are available for clinical use, and they differ a lot when it comes to their molecular structure, but they are kept rather similar in their colloid osmotic properties. Usually, these fluids are nearly isoosmotic, with the exception of 7.5% saline in 6% dextran, in which dextran is added to prolong the intravascular retention time³⁵⁻³⁷.

Current guidelines for fluid dosing in medical textbooks are given with little consideration of the effect duration over time and with little concern for the influence, in terms of the exact mechanism, that the condition of the patient exerts on fluid disposition and elimination. Studies conducted to answer the question of dosing typically uses the method of isotope dispersal³⁵⁻³⁷ or physiologic restoration end points³⁸⁻⁴¹. For the dispersal methods, it is taken as evidence that the results and recommendations for fluids that resemble the extracellular fluid correlate with the assumed extracellular volume. This means that if the plasma volume accounts for a

1/5 of the total extracellular fluid, accordingly, 1/5 of the administered fluid is supposed to be allocated to the plasma fraction – which is a erroneous assumption in fluid therapy. Since physiologic end points can be said to represent the efficacy and, as such, constitutes god end points, although they do not provide any information on intravascular volumes, volume shifts, or the functional mechanisms behind fluid dynamic differences. As for dispersal methods, the implicit presumption is that the obtained volume for tracer dispersal reflects the volume that is expanded by an i.v. infusion. The first presentation of volume kinetics⁸ pointed out the need for modeling with expandable body fluid spaces. Volume kinetics is aimed at pin-pointing the *functional mechanism* behind fluid dynamics and its alteration when it occur, and gives the user a *time resolution*. It should be remembered that volume kinetics, although depending on the model structure, does not use the blood volume (which is not determined), except for the correcting the reduced amount of point attractor resulting from blood sampling. and this is only a minor correction in which an estimation of the blood volume is used⁴².

Dispersal allows a tracer water (deuterium) molecule to interchange with a normal water molecule. The calculated result on extrapolating the dispersal volume at time zero yields the volume that was accessible for such dispersal. If an interchange of molecules takes place in areas where each water molecule is exchanged and no net accumulation occurs, no volume effect is obtained. If, however, a tracer water molecule is added in the current space, a net effect is occurs. If 1 L of labeled water is infused and it disperses in the total extracellular fluid space, amounting to 20 L in a fictive person, this will result in a total extracellular volume of 20 + 1 L. This is the fluid space to be detected by the tracer technique. Since 1 L is infused, it is subtracted from the volume obtained, giving the extrapolated value of 20 L. One liter expanded 20 L and resulted in a 5% expansion. If, however, 50% (10 L) of the extracellular volume is constrained by an internal network filament, as in bone and the gel part of the general interstitial matrix⁴³, or by surrounding impediments to expansion, as the kidney capsule or skull bone around the brain, these areas will be difficult to expand by an infused fluid volume, although the dispersal will occur into these tissues. Now, the remaining 50% or 10 L of extracellular tissue that is not constrained will expand from 10 to 11 L, subtracting 1 L results in an expandable volume of 10 L. Here we have an expansion of 10 % if a tracer that does not penetrate into *nonexpandable*

tissue is used. This is twice as much as that yielded by the dispersal method. Measuring the expandable fluid space is accomplished by using a substance that is present within the expandable space, and thus is diluted from an i.v. infusion. Such point attractor is available in the body: endogenous hemoglobin or albumin, and it might also be possible to use other substances, endogenous or artificial. The difference in the above example ranges from 10 L indicated by a volume kinetic approach and 20 L as indicated by a tracer model in the same fictive experiment, which constitutes an essential point and difference in what results are actually produced.

This thesis also comprises a noncompartmental approach (paper V) for allowing an extended comparison between solutions when different models must be used. It is a limiting fact that at this point, even though paper III provides a very useful tool, experiments are better described by VOFS1, VOFS2 or VOFS2_{ur}, alternatively, when crystalloids are used (papers II-V). Therefore, the comparison in paper IV was based on the mean of the obtained parameter results, and a few experiments in which the VOFS2 model was not solved were then omitted when creating the nomogram. Another approach is used in paper V for the creation of simulation curves that represent a group. All individuals curves were simulated and these curves were based on the individually selected model. Then the mean of the Y value (dilution) of the curve at each point in time was calculated and resulted in one representative group curve. When pooling of parameter results is used in volume kinetics, simulations are visually better fitted to the clustered measurement curves when the mean, and not the median parameters are used (unpublished simulations). The difference is small, and the cause of this is suggested to be a result of the integrated effect of parameters that always exists and makes them act almost pairwise.

It is shown in paper I that regional anesthesia affects the resulting dilution time curves from an i.v. infusion of crystalloid solution and that hemodilution curves can be used as indicators of volume changes over time. In paper I, the volume effect is calculated and presented as the percentage of the administered fluid that is retained. The important finding was that the condition of the patient (normotension, hypotension) strongly influenced the propensity of fluid to be allocated intravascularly. The time relation between the development of hypotension and dilution suggests that

hypotension is required for intravascular disposition of an i.v. fluid. This is not in perfect agreement with the common routine of giving 500 mL or more of Ringer's solution before the induction of anesthesia⁴⁴. It seems as if fluid should be administered during the limited time for anesthetic spreading (< 20 minutes). However, the current routine may reassure that hypovolemia is not present as this constitutes an immense risk for circulatory insufficiency during induction of anesthesia end points⁴⁵. Fluid could be recruited from other sources than an i.v. load⁴⁶ during hemorrhage, but this is not demonstrated in regional anesthesia⁴⁷. The heart rate increased in both groups during the first onset of anesthesia, but it is normalized to the baseline level in the hypotensive group. The heart rate remained elevated in the normotensive group. Since the analgesic spread was more pronounced in this group, the cardiac output was probably also more reduced in this group due to both a diminished venous return and a reduced heart rate, resulting from a cephalic spread of nervous block offsetting the heart pace fibers together with widespread vasodilation. A centralized fluid disposition could result from a reduced cardiac output. Since the cardiac output is more than 100 times the infusion rate, this does not explain the differences in hemodilution between the groups.

The ability of an i.v. fluid to dilute plasma was also considered in paper II, which was mainly aimed at confirming that the parameter results, using a variety of infusion rates and volumes, were stable. Stability is required if the results are to be used in simulations. Simulations are only valid within the performed ranges. Stability also serves as an indication of the validity of the model: a reasonable model structure can predict outcome in extended applications (infusion volumes and rates). Paper II was the first publication using volume kinetics in volunteers. The parameter results in paper II were very similar in all groups, the one exception being the most rapid infusion, in which the resulting unstressed volume was higher. This coincided with symptoms from the volunteers and is suggested to be an effect of too rapid an infusion in which the infusion itself increased the central body fluid space.

The measured urine volume corresponded well to the model prediction ($r = 0.83$), which serves as an indication of model validity. Some other crucial results were obtained. One was that the elimination was markedly exponential and the predicted intravascular fraction of 20% of the administered dose (common textbook statement)

was not attained until 30 minutes after ending the infusion. Until then, more fluid was retained in the circulation. A second finding was that the obtained unstressed volume (V or $V_1 + V_2$) was about 40% of the expected extracellular volume. A third result was that during this normovolemic infusion, the increase in the intravascular volume reached about 0.5 L in all 25 mL/kg infusions, and 0.25 in the 12.5 mL/kg infusions. 0.5 L is perhaps a limit where the intravascular compliance is stretched to confinement, considering that the most aggressive infusion also resulted in an intravascular volume effect of about 0.5 L, and that the excessive fluid sooner expanded the unstressed volume.

In addition, because of exponential relationships, it takes an exponentially increasing infusion rate to dilute each following fraction, or in other words, it becomes progressively more difficult to reach an intended dilution step, because the elimination increases progressively. The efficiency of the infusions declined in an orderly manner, with the lowest infusion rate being the most dose-efficient.

Assuming that the one exception to stability, was the rather larger unstressed volumes obtained in paper II, was due to the rapid infusion which exceeded the possible increase intravascular volume and opened up the extracellular areas that are normally not very compliant (the difference between the extracellular space and the obtained unstressed volume, i.e. V , or $V_1 + V_2 - \text{extracellular volume}$). This could decrease the albumin exclusion space^{48, 49} and thus increase the compliance in the extravascular and extracellular space. The symptoms that were reported during the rapid infusion may be explained by such altered fluid handling.

In paper II, a problem arose that was successfully addressed in paper III: Some curves belonged to the VOFS2 model, which unfortunately failed to provide acceptable parameter results. The explanation for this can only be speculated on. In the analysis for model selection, a robust and frequently used F test was applied (papers II-V). The F test is known to have a preference for the simplest model, compared to other model selection algorithms.

F test uses the *degree of freedom* in the calculation and the degree of freedom is partly obtained from the subtraction of the number of parameters from the measurement

points. When increasing the parameters from two to four, the ratio of the number of parameters to the number of measuring points increases and a step from two to four parameters becomes especially apparent if a low number of measurement points are being used. Increasing the measurement points and also the addition of a simultaneous new point attractor, the red cell count (paper V), did increase the precision in outcome.

The use of urinary volume to calculate k_r (paper III, VOFS2_{ur}) was not a practicable model for all experiments. MSQ increased in general using this model, which is to be expected because reducing the estimated parameters in the VOFS2 model from four to three reduces the possible shapes that the resulting curve could have. Additionally, the use of measured urine failed completely in the VOFS1 model since it constrained the possible shapes too much (each parameter included in the analysis could be regarded as being a joint for motion, and the more joints, the better the capability of adapting the curve to the data). When using albumin, the probability of a VOFS2 F test selection increased (papers III-VI), which is thought to be an artifact loss of intravascular albumin. (see below). The central volume, V1, did not differ between the noncompartmental k_r calculation and the original VOFS2 model, but the V2 increased and the k_r was reduced significantly when the noncompartmental k_r calculation was used (paper III). When k_r in both models agreed, a V2 of about 10 L was detected, which indicates that the peripheral volume is smaller than the expected extracellular volume.

The noncompartmental and the compartmental calculations of k_r differ. The first is determined by the area under the dilution curve and the second is determined by the terminal slope of the curve, and therefore they might produce different results. The fact that using urine volume-based k_r calculation did not improve the model outcome in general, suggests that further investigation is desirable. The content of sodium is probably important for how urine volume correlates with the elimination. The VOFS2_{ur} model was a good method in selected cases where the F test showed that a two compartment model was appropriate but the VOFS2 model produced intercorrelated results.

In paper VI, all the compartmental models (VOFS1, VOFS2, and VOFS2_{ur}) were used to demonstrate what mechanisms are involved when fluid handling is altered by hemorrhage, which is a common clinical situation. After obtaining the parameter results for the hemorrhagic loss of 450 mL, 900 mL, and no hemorrhagic loss, a nomogram was constructed for the purpose of providing a guide for resuscitation. The obtained dilution time curves corresponded well with the measured plots (Fig. 2, paper VI). Increasing hemorrhage resulted in an increase in dilution. When albumin was used all experiments could be fitted to the VOFS2 model, whereas the use of hemoglobin could fit all experiments in the 900 mL group to the VOFS2 model but only 80% in the other ones fitted the VOFS2 model. The parameter that controlled the handling of fluid was k_r which decreased from 28 in the control experiments to 19, and 6 when 450 or 900 mL was withdrawn. V_1 tended to decrease by about the same amount as the plasma loss, indicating that the central fluid space correlated with the plasma volume. The nomogram was based on the parameters obtained with the VOFS2 model as this was the most frequent outcome. It is not possible to use the mean parameters from analyses in different models; therefore, the result from the most frequently selected model was used. In paper V, however, this problem was addressed in another way: here simulation was individually done using the most appropriate model. Subsequently, the mean dilution from all curves was calculated at each time point, and the resulting dilution curve for each group was then a mean of all individuals. Here, no pooling of parameters is for group specific simulation.

The nomogram for hemorrhage provides information on how to reach a predetermined level of dilution and what rate is needed to maintain the dilution over 30 minutes. A specified time interval for maintaining the dilution, was chosen because the nonlinear model used results in concave curves, and not straight lines, thereby producing variation over time. Therefore, there is a certain overestimation in the interval from the time point for reaching the dilution to 30 minutes afterwards. However, when an individual has reached a steady state by i.v. infusion, the infusion rate to maintain the dilution theoretically equals the rate of elimination.

In paper V, modeling by both compartmental and noncompartmental routines was used. The selected infusion volumes were set to produce a dilution of about 20%, which was accomplished approximately (no precise guidance was found in the

literature). The use of volume kinetics to compare the dilution effect of fluids increases the precision in the comparison since the individual regression curves can be simulated to reach a similar dilution in all groups and the curves simulated curves do not have the noise that is present when comparing measurement points. A regression curve is a kind of mean of all measuring points. Therefore, no noise is present in and fewer experiments can be compared since the variation in each point selected for comparison is reduced. To compare fluids, only one way of comparing is not sufficient. To conclude that one fluid is 20% more effective than another fluid does not take into account that differences in dynamics influence the effect in different ways. Reaching a dilution is one issue and the following dilution effect (during elimination) is another one and the resulting overall dilution (area under the curve) is yet another issue. The noncompartmental approach allows some comparisons to be made regardless of the underlying compartmental structure. The noncompartmental modeling has not been consistently used for the purpose of infusion fluid dilution effect evaluation. However, the use of a urine volume measurement for k_r calculation (paper III) constitutes a noncompartmental sub-routine.

The noncompartmental approach revealed that, for isotonic solutions, which are generally considered to be equivalent, normal saline was almost 20% as effective in diluting the plasma as were both Ringer's solutions during the 240-minute observation period, although Ringer's acetate leveled off at a similar degree of dilution at the end of the simulation as for normal saline, indicating that (according to the resulting slope of the curve), Ringer's acetate had the most pronounced long-term effect. The volume kinetic analysis showed that to reach a 20% dilution, Ringer's acetate was 14% less potent than normal saline or Ringer's lactate.

A new three compartment model was developed for the modeling of hypertonic fluids to include the volume shifts that occur as the hypertonicity of the infusion fluid attracts fluid from remote areas in the body. Fluid also returns to the remote areas when the infusion load of osmoles are withdrawn. Two fluids are currently in use, 7.5% saline and 7.5% saline in dextran which is added to increase the plasma retention time. Hypertonic saline was 3.7 times as effective as normal saline in reaching a 20% dilution. These results showed that the increase in duration from the

addition of dextran, was a result of direct effect enhancement of the dilution. Dextran did not alter the elimination slope of the curve in a notable way.

Modeling hypertonic solutions required the urine volume input model, in all experiments. For the dextran-containing fluid, the two volume model fitted all experiments and for 7.5% saline, the same model fitted 6/10 of the cases. When the three-volume model was selected, the resulting central fluid volume was smaller than the expected plasma volume. The only reason for such a smaller volume is that there is a detectable time difference in the stirring of the plasma. The lower extremities are equipped with venous reservoirs for adjusting the venous return during exercise and hemorrhage, which is not as pronounced in the shorter vessel systems of the upper body. Thus, the turnover rate might differ between the lower and upper body and produce a detectable time lap between equilibration in the lower and upper body, resulting in central volumes that are smaller than the plasma volume.

To illustrate what long-term effect could be expected from an increase in dose, a new concept, "time gain" was introduced (Fig. 5, paper V). Taking two differently acting solutions, normal saline and 7.5% saline, it is shown that when the infusion volume is increased from a resulting end-of-infusion dilution of 15% to a dilution of 30%, the time it takes until the dilution in the high dilution curve goes back to the dilution in the low-dilution curve, at the times 30, 60, 90, 150, and 200 minutes is clearly dependent on the descent of the slope of the curve. This means that for a fluid to benefit in effect over a prolonged time, it should not undergo rapid elimination as 7.5% saline does. Such considerations are common in drug dosing, which is the underlying reason for some drugs to be recommended to be taken three times daily, and others only once daily. However, such a conclusion is not a common consideration for anesthesiologists in their fluid therapy decisions.

From dilution to volume

Volume kinetic simulations are basically presented as dilution time curves because they comprise the fewest assumptions. However, the obtained dilution can be transformed to volumes. If the resulting dilution curve is multiplied by the unstressed central volume, the volume time curve is obtained. If the central volume correlates with the plasma volume, this gives the plasma volume change over time. However, if

the central volume is larger than the central volume, all the volume that is expanded in the central volume does not expand the plasma volume. If a plasma volume change over time is desired and the central volume does not correspond to the plasma volume, it is possible to multiply the dilution by the plasma volume (as calculated from body weight or measured). When multiplying the dilution by the V , the model resembles a turnover type.

By introducing a turnover concept in volume kinetics new illustrative parameters could be derived. Here is a comparison between the elimination equations in pharmacokinetics and volume kinetics. First the pharmacokinetic equation:

$$\text{Excretion ratio (mg/min)} = \text{Clearance (mL/min)} * \text{concentration (mg/mL)}$$

is represented by the following equation in volume kinetics:

$$\text{Excretion ratio (mL/min)} = k_r \text{ (mL/min)} * (v-V)/V \text{ (no sort)}$$

If, in volume kinetics, the dilution $[(v-V)/V]$, by an easily performed rearrangement, is instead represented by the amount $(v-V)$, the formula becomes:

$$\text{Excretion ratio (mL/min)} = k_r/V \text{ (1/min)} * (v-V) \text{ (mL)}$$

And the slope of the elimination curve is described by k_r/V , which represents a turnover model, which in turn gives the opportunity to perform further calculations used for turnover models (Cl could then be replaced by k_r for modeling of turnover of fluid) as:

$$\text{Turnover time} = V / Cl$$

$$\text{Half life} = \ln 2 * V / Cl$$

$$\text{Baseline} = k_i * V / \text{Cl}$$

$$\text{Steady state} = k_i * V / \text{Cl}$$

The resemblance between a turnover model and a response model is very close⁵⁰.

Can the volume kinetic model be improved?

When dealing with volume kinetics the estimation of the resulting dilution dependent elimination (urine) could also be an effect parameter which would then be better described by a urine-volume dynamic model (adapted to volume kinetics) based on a modified Hill equation⁵¹. The reason is that the production of urine is under hormonal control, and may not then be directly related only to the dilution⁹⁷. Another issue in volume kinetics is that the content of sodium in the urine produced in the current model is not accounted for, which may influence the kinetics. If the urine is isotonic, no corrections have to be made. If the urine is hypotonic, part of the produced urine volume would originate from a remote fluid space, and if the urine is hypertonic, some fluid must be allocated from the central body fluid space to the remote fluid space. In this situation, the current model would estimate the whole fluid loss from the central compartment, but all of this is not represented by the urine volume.

Are both the VOFS1 and VOFS2 models needed?

In general it would be convenient to manage crystalloid experiments according to the VOFS2 model, for the purpose of comparative studies. It is convenient and straightforward to compare the parameters between groups, without the complication of alternating models. For example, the elimination rate cannot be taken out of its context and relation to the other parameters, especially if different models are being used. The resulting volume elimination from the system is dependent on both the dilution and the elimination rate constant. Therefore it is not sufficient just to compare the elimination rate constants of two experiments since elimination also scales to the unstressed volume. Theoretically, it should be possible to manage all dilution curves from isotonic experiments with the VOFS2 model.

New approaches

If V2 should approach zero as fluid is handled increasingly more like a VOFS1 model, the VOFS2 model should be able to detect these curves as a VOFS2 curve with a small peripheral space. However, this is not seen in our experiments. On the contrary, the peripheral fluid volume had a tendency to assume galloping V2 values when the VOFS1 model was justified. Here one explanation could be the fixed k_t . Considering that the rate of fluid is governed by ratio of the dilutions between two compartments, and the rate constant, which is k_t between compartments, is the same in both directions the result is that the unstressed volumes in both compartments can not be too different if a notable net flux of fluid is going to bounce between these spaces. If the bouncing volume leaves and returns to the central space this overflow volume is not too different between the spaces, $(v1-V1)$, $(v2-V2)$. If V1 is considerably larger than V2 the bouncing volume would relate to V2 differently than to V1. This suggests that when using k_t the overflow volume in V2 would outscale the same volume in V1 producing a strong vector for the flow from the V2 space. This might be the reason for the current model not to detect small secondary fluid spaces. What happens instead is that the algorithm tries to find a V2 that corresponds to the assumed bouncing volume instead and causes the model to deviate the V2 to large values.

Two alternative approaches may solve this problem. One is to reduce the estimated parameters in a novel way, (different from the VOFS2_{ur} model) the other approach is to subdivide k_t into its two directions. To reduce the number of estimated parameters in the VOFS2 model from four to three would increase the probability of successfully managing the model for all experiments. Another way to manage a general VOFS2 analysis is to release k_t from its constraints even if this actually increases the amount of parameters. A new model version in which k_t is divided into its two components is in progress. If five parameters prove to be too many such model can be used with input of the urinary volume to reduce parameter from five to four again.

When fixing k_t in its group mean value for crystalloid solutions (which was about 300 from the cases that are properly solved in the VOFS2 model, unpublished data) a series of 15 cases were all solved. Only 12 of these were properly solved by the existing VOFS2 and VOFS2_{ur} models. Small V2 volumes were also detected. The rationale for this is the finding that k_t is the parameter that contains the least

correlation with the other parameters, whereby fixing it little influences the remaining parameters. In addition k_t is the parameter that contains the smallest amount of information since it might be regarded as a fusion of two parameters. Possibly, k_t also depends largely on the blood flow, i.e. the cardiac output more than some tissue related fluid volume exchange factor (vascular perviousity or matrix structure rearrangement inducing flow rate shifts).

The VOFS2 model in its current version uses the same compliance relationships for v_1 and v_2 , the exponents (a) being 1 $[(v-V)^a/V]$. The vascular system has a limit for what volume it may contain because of limiting structures in the vessels wall. In contrast, it has been demonstrated that the interstitial space can hold huge amounts of water, with the interstitial pressure reaching and leveling off at a pressure of about 2 cm of water despite continued volume load. Dogs have been resuscitated with 20% of their body weight⁵² and most of the fluid is supposed to be allocated in the interstitial space. Another indication of an inverse compliance is given by the albumin exclusion resulting from an i.v fluid load¹². When the interstitial fluid volume is increased, the matrix is stretched apart and molecular microfilaments, such as glycosaminoglycans and proteoglycans, are separated, and increase the space for free fluid movement. The molecular connecting forces are reduced by the distance between filaments¹².

An alternative explanation for why the VOFS2 model sometimes fails to produce precise estimates in crystalloid experiments is that the inherent model-to-reality aberration is the source of error, which is supported by the finding (papers II-V) that dilution time curves often dip at about 30 minutes after ending the infusion. Such systematic deviation probably reflects a biological feedback regulating loop, producing a sinusoidal curve that is amplitude-damped over time. At the present time, this occurrence has not been explored. A program to examine this sinusoidal propensity by frequency-finding algorithms has been initiated. Still, supposedly this will not eliminate all sources of distorted precision. The author has also examined the effect of returning the output curve data from simulations back to the analysis process and found that even if a defined set of parameters are used in simulation, the return of the data points into a new curve fit procedure, will not provide perfect and unbiased

estimates, suggesting that there could be a loss of precision in the least square algorithm used.

Another approach examined, but not published, was to try different weights in the regression algorithm. There are many different types of weighting, the common purpose being to offset the influence of some sources of error that occur systematic. The error of a measured parameter Y may increase in relation to the Y value. If such error is present, a reduction of this error can be introduced by a factor of $1/Y$ or even $1/Y^2$ in the minimization process. Even more common is to use \hat{Y} (predicted Y) instead of Y . Several weighting models were examined including $1/Y^{1 \text{ and } 2}$ and $1/\hat{Y}^{1 \text{ and } 2}$. Y was also replaced by the group variance found in each measurement points. In general, weights altered the outcome but they also reduced the unstressed volumes by squeezing the curves downwards while the high Y values was given less weight.

The special feature of volume kinetics incorporated in the crucial formula $v-V/V$ allows a random oscillation around zero which typically occurs when the baseline is reached during the late phase of an experiment. This is usually not seen in pharmacokinetics since concentration measurements rarely oscillate around zero. Negative concentrations are not seen, which reduces the error when Y approaches zero in pharmacokinetics, but not in volume kinetics, suggesting that any $1/Y$ type of weighting is inappropriate here. The prerequisites for weighting in volume kinetics was elucidated by performing thousands of simulations on the dilution formula ($v-V/V = X-x/X$) using arbitrary values for X and x , combined with an introduction of noise at various degrees (unpublished data). The distribution of error become skewed only when dilution is extreme and out of relevant proportion (i.e. low V to v ratio) in combination with marked noise of more than 15% of v .

The role of k_b has also tested and it was concluded that introducing a 50% variation in k_b affected the parameters by 10%. The k_b is calculation from the expected loss of fluid from perspiration and spontaneous diuresis. The magnitude of this fluid shift was obtained from other publications⁵³. The used application of k_b seems to be correct and it could be argued that k_b in the current model is withdrawn from V or $V1$ directly and completely. The water evaporated from the body (free water) may originate from the whole fluid volume and not specifically from the central compartment. If so, k_b

which is acting from the central compartment should be reduced by the proportion that exists between the estimated total body water and the V or V1.

Slightly different k_b have been used in this thesis. This depends on how much fluid is given back in order to flush the cannula clean and if the subjects were allowed to drink in the morning or not.

The Ringer's solutions

Crystalliod solutions have been in use in fluid therapy for over a century and they are considered safe, nontoxic, and free of adverse reactions. It was concluded early on that there was a need for salt in the replacement fluids. The desired composition was estimated from the measured losses during illness and surgery and to mimic the plasma fluid salt content seemed obvious. However, this sodium content frequently seems to fail to compensate for the hormonal fluid and salt regulating adaptations in the postoperative setting⁵⁴. The common state of acidosis in states of critical illness pointed towards a need for a buffer system in resuscitation fluids. And so the weak buffer lactate was added and Ringer's solution was created. Although added substances do have pharmacological properties, fluids are not generally accepted as drugs. However, fluid composition has a role in body fluid handling with a potential risk of side effects. One example related to plain sodium is the well-known risk of iatrogenic pontine demyelination induced by rapid treatment of severe chronic sodium deficiencies. Another is the complication of pulmonary edema resulting from excess fluid therapy.

In Scandinavia, lactate is replaced with acetate. Acetate is metabolized in the plasma and lactate is metabolized mainly in the liver, which makes acetate advantageous if the receiver has a compromised liver function or is in a state of shock that reduces the liver blood flow and hence the lactate content could theoretically aggravate lactic acidosis. Acetate is generated by bacteria in the body at low concentrations in the gut⁵⁵ and in peripheral tissue during exercise and is suggested to be produced for redistribution of oxidizable⁵⁶ substrates throughout the body.

Cations like K^+ , Mg^{2+} , and Ca^{2+} are vasoactive, whereas most anions are not. However, lactate and acetate possess pharmacological properties, the most prominent

being vasodilatory activity. Acetate induces vasodilation^{57, 58, 59, 60} presumably by a reduced tissue ATP/adenosine quotient. Negative inotropism has been described in isolated heart muscle preparations due to impaired fatty acid metabolism⁶¹ and during hemodialysis in humans⁶²⁻⁶⁴ and could be reversed by the administering of glucose⁶⁵. This effect is considered to be independent of calcium complexing, osmolality or sodium concentration⁶⁶, and positive inotropism^{67, 58}. Acetate and lactate activate the immune system, increasing the number of circulating leukocytes, and acetate has been shown to increase peripheral tissue metabolism beneficially^{68, 60}, and it reduces the respiratory drive by increasing the extrapulmonary loss of CO₂. Lactate, on the other hand, can enter the neuronal aerobic metabolism through conversion to pyruvate⁶⁹ and be used in preference to glucose and thereby reduce the ischemia/reperfusion injury⁷⁰. Lactate can also elicit the acute panic syndrome, especially in predisposed people, and has been used as a model for research on panic disorders and flashbacks⁷¹⁻⁷³. Lactate has also been found to induce neutrophil activation after hemorrhagic shock⁷⁴ and acetate infusion caused immune activation in mice⁷⁵ and humans⁷⁶. The majority of countries use Ringer's lactate. No convincing evidence for aggravation of lactic acidosis even in liver malfunctioning patients has been presented. Hemodynamic effects of solutions containing acetate or lactate are not strong enough to show differences in clinical studies⁷⁷.

Acetate has some theoretical benefits over lactate, and D-lactate has been suggested to be eliminated from i.v. fluids and the content of L-lactate has been suggested to be reduced⁷. The use of fluids that interact with the immune system may blur the interpretation of immunologically related research, which has to be taken into consideration, especially since the term "Ringer's solution" actually refers to the acetate compound in Scandinavia. Acetate has been associated with vascular side effects originating from its vasodilatory action. Regional blood flow is redistributed by vasodilation, directing the flow towards the splanchnic region⁷⁸. It seems contradictory to use a fluid, to volume-compensate for the vasodilation induced by anesthesia when the fluid itself is a vasodilator which might counteract the compensatory vasoconstriction.

Acetate has been associated with positive inotropism from utilization of ATP in both whole-animal and in vitro vascular preparations⁷⁹⁻⁸¹ and negative inotropism during

dialysis⁸²⁻⁸⁴. The uncertainty of whether acetate is a positive or negative inotropic compound is probably explained by the fact that direct heart muscle effects are canceled out by improved systemic regulation of the venous return. Bench-testing of isolated heart muscle demonstrates negative inotropism, and in vivo experiments result in positive inotropism, in which the intact animal vasodilates, which results in an improved venous return and thus an increased cardiac output often with maintained blood pressure although the cardiac muscle is slightly impeded by the compound.

Actions that occur in the systemic circulation may very well alter the volume kinetic parameter results. For example, spinal anesthesia (unpublished data) is associated with smaller central unstressed volumes, reduced elimination and a tendency to VOFS2 F test selection. Knowing that pharmacological action on the vascular system may alter the disposition and elimination of i.v. fluid, and that molecular components in fluids possess such action, a comparison of different isotonic crystalloid solutions was warranted and, consequently, undertaken in paper V.

Hypertonic solutions

In paper V, the comparison between fluids also comprised 7.5% hypertonic saline and 7.5% hypertonic saline in 6% dextran. The first compound is currently recommended as a rapid bolus of 250 ml for the resuscitation of hemorrhaging battlefield victims⁷. Hypertonic saline solutions are known to restore circulation after hemorrhage when small rapid volumes of about 1:10 of the shed volume are infused^{85, 90-94}. Dextran is a naturally occurring glucose polymere molecule produced by the bacterium *Leuconostoc bacteroides*⁸⁶. Dextran can be found in dental plaque and food and is formed on sucrose by the enzyme sucrase. Its viscosity is between that of plasma and blood, while its specific gravity is slightly greater than that of plasma. It possesses a high colloid-osmotic (oncotic) pressure. Dextran was originally prepared in Sweden and was suggested as a plasma expander in 1944 by Grönwall and Ingelman⁸⁷ and consists of polysacharides with glucose units joined by alpha-1:6 linkages.

Temperature

The temperature of the infused fluid affects body fluid handling properties. A comparison of infused Ringer's acetate showed that warm (36°C) infusion in volumes and at rates comparable to what was used in this thesis did not change the heart rate or

blood pressure but decreased the colloid osmotic pressure insignificantly. However, cold (18°C) infusion increased blood pressure, the atrial natriuretic factor, and diuresis. No difference in dilution properties was found. This suggests a leakage of plasma proteins from the vascular circuit when warm Ringer's solution is infused^{88, 89}. Such differences probably could affect the volume kinetic results. Therefore, the ambient room temperature (20-22°C) was used for the infusates throughout this thesis.

FUTURE PROSPECTIVE FOR VOLUME KINETICS

The current objective in volume kinetics should be to improve the estimation of parameters in order to achieve a generalized outcome with one model when isotonic fluids are used. The advantage of using a uniform model is that the parameter results can be compared directly, both in settings where individual changes are produced by experimental conditions such as anesthesia, sepsis, hemorrhage, and dehydration, and also in studies aimed at understanding fluid handling differences between patient groups and at a better understanding of how fluid composition and different treatments affect fluid distribution and elimination.

One company (Sangart, inc., San Diego), which is working on the development of artificial blood – a blood substitute consisting of cell-free hemoglobin encapsulated molecule by molecule in polyethyleneglycol chains – is seeking volume kinetic guidance in their attempt in calculating the real elimination rate for their substance, realizing that their product, by virtue of its hyperoncotic pressure, alters the intravascular fluid content, which makes a classical approach inappropriate.

Another matter to examine is the question of at what point in time is the real baseline level reflected? When the dilution is changed during an experiment the baseline could be accepted as the dilution at the beginning or at infinity time. In this thesis generally the zero time point was considered as the baseline. However, it is possible to use another criterion although this gives rise many more assumptions. During hemorrhage the body strives to maintain the blood volume, which induces a dilution when this is achieved. At this point, the driving force $v-V/V$ does not produce an elimination since the blood volume is restored, although dilution is present. The use of a restored blood volume would not be fully appropriate either since the altered composition of plasma and interstitial body fluid probably changed the equilibrium between these spaces, making the real baseline dilution a guess. A better approach may be to use a derivative of the time-dilution curve, setting the baseline to be within for example, a

derivative of 10% from zero over four consecutive measurements. However, even such an approach has its disadvantages. How does the baseline evolve upon reaching this? Does it follow a straight line over the experiment or is it an exponential function or perhaps it is a straight line during infusion turning into a horizontal line from the end of the infusion? Such model adjustments have to be addressed in separate, well-defined settings.

Model improvements could be made using the sequential urinary volume and urinary and plasma content of solutes and their ability to cross membranes for estimating cellular fluid shifts. A large urinary proportion of solutes that do not cross a membrane causes an intracellularly directed fluid shift, whereas hypotonic urine would be partly derived from outside the extracellular fluid spaces.

CONCLUSION

Fluid is handled dynamically in the body. Hypotension and hemorrhage results in central allocation of i.v. fluid. To better understand and illustrate mechanisms behind fluid dispersal and elimination, volume kinetics was developed and introduced in 1997. The important conclusion that hemoglobin is a useful point attractor for the necessary input of a dilution, was arrived at in Stockholm, and presented in 1997. The next breakthrough in volume kinetics was to show that using different infusion volumes and rates resulted in similar parameter results, which was made in paper (II). However, it was not possible to analyze some experiments strictly according to the VOFS2 model, although the F test showed that this model was justified. Therefore, paper III was aimed at reducing the number of parameters in the estimation process from four to three in an attempt to increase the precision of the estimates. This was successful in the selected cases where a problem was present. It was not, however, a method for general use. It is concluded that even if this approach represents a noncompartmental routine, it is better to use it than to accept the VOFS1 model when the curve fit notably deviates. In paper IV, volume kinetics was used to device of a nomogram for resuscitation after hemorrhage. In addition, it was shown that the main mechanism for preserving fluid in the body during hemorrhage is diminished urine excretion, and not changes in body fluid spaces. The most recent work (paper V), compared iso- and hypertonic fluids and it was concluded that more than one approach is required to describe and understand their dynamics. Clearly, hypertonic solutions had the best dose effect. However, dextran did not really change the elimination slope as was expected. It is necessary for the user of i.v. fluids to understand the dynamics of fluids when dosing is considered.

Volume kinetic modeling serves as a very useful tool in the modeling and understanding of fluid dynamics. Many sidetracks must be investigated and the modeling must be further tuned, however, considering that pharmacokinetics has evolved over decades and that pharmacokinetics has been used by so many clinicians, researchers, and institutions worldwide, it is a task that is greater than one or just a few research centers can possibly handle.

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