Thesis for doctoral degree (Ph.D.) 2010

Mathematical modelling of clinical applications in fluid therapy

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Karolinska Institutet

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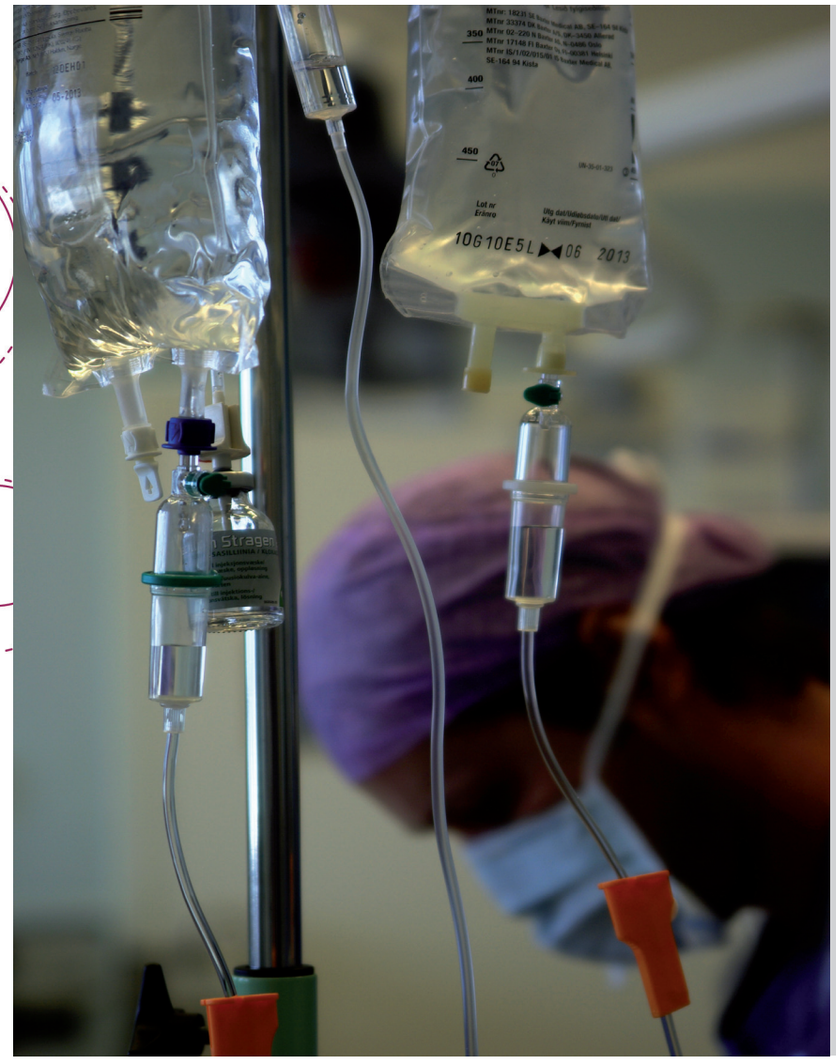

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Tjáhtje le iellem

"Water is life" in the Lule Sami language
Spoken by approximately 500 in the world.

This thesis is dedicated to my wife Annika and to my children,
Karolina, Felix and Matilda.

LIST OF PUBLICATIONS

This thesis is based on the following publications, which will be referred to in the text by the Roman numerals:

I. Hahn RG, Brauer L, *Rodhe P*, Svensen C, Prough DS. Isoflurane Inhibits Compensatory Intravascular Volume Expansion After Haemorrhage in Sheep. *Anesthesia & Analgesia.* 2006; 103: 350-358. [1]

II. Svensen C, Olsson J, *Rodhe P*, Boersheim E, Aarsland A, Hahn RG. Arteriovenous Differences in Plasma Dilution and the Kinetics of Lactated Ringer's Solution. *Anesthesia & Analgesia* 2009. 108: 128-33. [2]

III. *Rodhe P*, Drobin D, Hahn RG, Wennberg B, Lindahl C, Sjöstrand F, Svensen C. Modelling of Peripheral Fluid Accumulation after a Crystalloid Bolus in Female Volunteers - a mathematical study. *Computational and Mathematical Methods in Medicine*. 2010, in press. [3]

IV. *Rodhe P*, Waldréus N, Svensen C, Wennberg B, Sjöstrand F. A Comparison of Fluid Distribution in Old and Young Volunteers Given 2.5% Glucose Solution either Orally or Intravenously. Manuscript. [4]

ABSTRACT

Mathematical modelling of clinical applications in fluid therapy

Background: This thesis presents a new application of fluid kinetic analysis using mathematical tools to evaluate fluid therapy problems. Several models were developed to mathematically handle fluid distribution concerning bleeding and anaesthesia, arterio-venous differences in plasma dilution, peripheral fluid accumulation and differences in fluid distribution among young and elderly patients. Non-linear regression models were used to fit equations to sampled haemoglobin data.

Methods: I: Six chronically instrumented sheep were subjected to four randomly ordered experiments while conscious or during anesthesia with isoflurane. After plasma volume measurement 15% or 45% of the blood volume was withdrawn. To quantify transcapillary refill, mass balance and kinetic calculations utilized repeated measurements of haemoglobin concentration. **II**: Fifteen volunteers received an intravenous (iv) infusion of 15 mL/kg of lactated Ringer's solution during 10 min. Simultaneous arterial and venous blood haemoglobin (Hb) samples were obtained and Hb concentrations measured. **III:** Ten healthy female non-pregnant volunteers participated. The protocol included an infusion of acetated Ringer's solution, 25 ml/kg over 30 minutes. Blood samples were repeatedly. A standard bladder catheter was continuously monitoring urine excretion. Plasma dilution, peripheral accumulation and urine output were modelled simultaneously. **IV:** Twenty four volunteers participated. Two age groups, a young group (age 18-25) and an elderly group (age 70-90) were formed. On separate occasions, the subjects in both groups were given a crystalloid 25 mg/ml glucose solution, either orally (ORAL) or intravenously (IV) in a crossover design with at least two weeks in between. On each occasion, the subjects got 7 ml/kg of the crystalloid solution during 15 minutes.

Results: I: After either normotensive or hypotensive hemorrhage, transcapillary refill occurred more rapidly during the first 40 min than during the next 140 min ($p < 0.001$). In conscious sheep, at 180 min, 57% and 42% of the bled volume had been restored after normotensive and hypotensive hemorrhage, respectively, in contrast to only 13% and 27% ($p < 0.001$) in isoflurane-anesthetized sheep. Using parameters derived from kinetic analysis, simulations illustrate that both the hydrostatic and colloid osmotic forces are weaker in the presence of isoflurane than in the awake state.

II: The AV difference in plasma dilution was only positive during the infusion and for 2.5 min thereafter, which represents the period of net flow of fluid from plasma to tissue. Kinetic analysis showed that volume expansion of the peripheral fluid space began to decrease 14 min (arterial blood) and 20 min (venous blood) after the infusion ended.

III: Maximum urinary output rate was found to be 19 (13 – 31) ml/min. The subjects were likely to accumulate three times as much of the infused fluid peripherally as centrally; Elimination efficacy, E_{eff}, was 24 (5 – 35) and the basal elimination k_b was 1.11 (0.28 – 2.90). The total time delay T_{tot} of urinary output was estimated to 17 (11 - 31) min.

IV: The lag-time of glucose given orally was estimated to be 17 (8 – 25) min for the younger group and 18 (13 – 22) min for the elderly. For fluid, the lag-time was estimated to 29 (21 - 34) min for the younger and 25 (16 – 39) min for the elderly.

Conclusions: Final conclusion is that mathematical modelling of clinical applications can be done in several different clinical settings and will improve the understanding of fluid distribution. It is possible to continuously model fluid behaviour in the body as seen in Papers II-III. This should enhance the understanding of accumulating oedema in the body which is an apparent problem for all clinicians.

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CONTENTS

LIST OF ABBREVIATIONS

ODE	Ordinary Differential Equation
PDE	Partial Differential Equation
TBW	Total Body Water (ml)
BW	Bodyweight (kg)
H	Height (m)
ECF	Extracellular Fluid (ml)
ICF	Intracellular Fluid (ml)
TBV	Total Blood Volume (ml)
EVF	Erythrocyte Volume Fraction (ml)
ECV	Erythrocyte Cell Volume (ml)
PV	Plasma Volume (ml)
Hct	Hematocrit

1 PREFACE

This PhD thesis was carried out and produced at the Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden, under the supervision of Christer Svensen. Current co-supervisors of the thesis are: Fredrik Sjöstrand and Bernt Wennberg. Previous co-supervisors have been Dan Drobin and Robert Hahn. The external mentor has been Lena Nilsson.

The research was mainly funded by the Department of Anaesthesia and Intensive Care, Södersjukhuset and the Department of Clinical Science and Education at Karolinska Institutet/Södersjukhuset.

2 SUMMARY

The main objective of this thesis is to develop the understanding of fluid therapy by the use of applied mathematics and to find appropriate clinical characteristics and physiological explanations by mathematical models.

The theoretical platform of fluid therapy has not widened as much as other clinical scientific fields [5]. Very much of fluid therapy is based on tradition and rules-of-thumb. One main issue is that a number of variables, which are essential to make a deeper assessment of the fluid status of a patient, cannot be measured accurately without significant intrusion in clinical practice.

Even though intravenous fluids should be classified as drugs since they are given in large amounts daily in hospitals and have great impact on outcomes of patients, they are commonly regarded merely as technical aids. Although fluids are part of daily clinical practice the scientific evidence behind their applications is weak. Therefore, clinicians are reluctant to change their routine practice [6].

However, the need for fluid resuscitation, treatment of dehydration and hypovolemia, and for correcting various pathological states that inflicts negatively on the outcome, acid-base levels, the microvascular perfusion, the oxygen transport and the osmotic balance, is pertinent [7].

Therefore there is need of more solid evidence for fluid applications in clinical practice.

The main conclusion of the thesis is that mathematical modelling may contribute to a better understanding of fluid distribution and eventually form more solid theoretical concepts.

3 BODY FLUID DYNAMICS – A BRIEF INTRODUCTION

A cold water spring in the north of Sweden

Water is one of the cornerstones of life. The water serves as a solute to dissolve other solutes and it transport nutrients, oxygen and other necessary compounds within and between cells [8]. Furthermore, water dissolved ions creates the cell membrane potential, which is crucial for almost all transport of solutes across the cell membrane [9]. Water is also a necessary component in almost all biochemical processes such as cell respiration and photosynthesis [10]. In fact, science today cannot predict or even imagine any life forms in the universe without the presence of water, even if there are some exotic guesses.

An adequate fluid and salt balance is therefore of a major importance for almost all basic and critical body processes, ranging from physiological functions to basic cell processes [9]. Even

a small perturbation of this balance will affect the well-being and even short-term survival of any living organism on earth.

3.1 TOTAL BODY WATER

The total body water (TBW) is the amount of water in the whole body, distributed through several compartments, commonly divided into the extracellular fluid space (ECF) and the intracellular fluid space (ICF) [10].

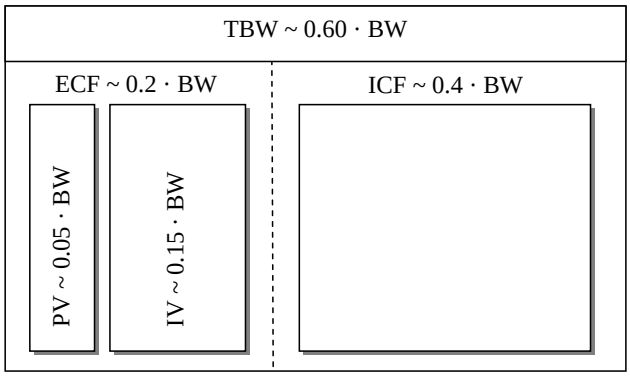


Figure 1. The fluid distribution in the body

The turnover rate of water for TBW varies greatly betweens individuals, and it depends highly on activity, temperature etc. However, a common estimation for adults, in a temperate environment, is that about 2 L/day is needed, corresponding to 5-10% in turnover rate of the TBW [11].

Our daily consumption of water is through oral intake, but a small amount of water is also produced within the cells as a result of the citric acid cycle. Water losses are through skin, respiration, urine, faeces and sweat, see Figure 2 as an example [10]. The basal loss of fluid per minute is about 0.5 - 1.5 ml/min for an average adult [12], an important parameter to consider in almost all clinical situations [13].

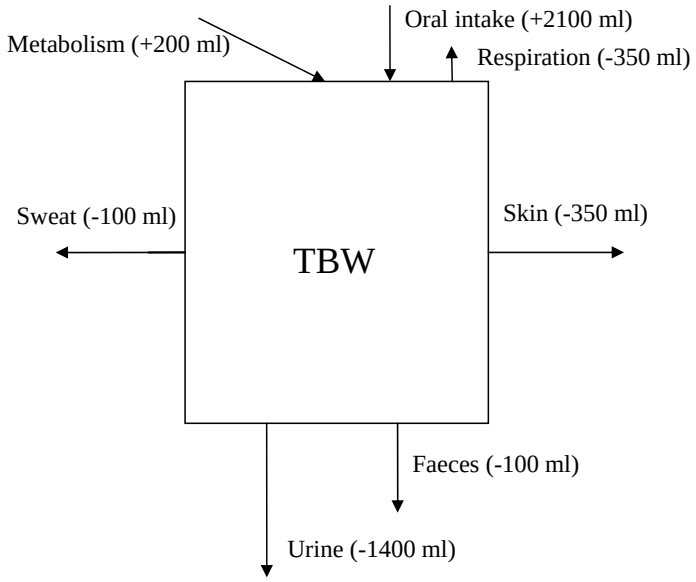


Figure 2. Example of a TBW daily turnover from [10].

Loss of only 5% of TBW, which corresponds to approximately 2.5 L for an adult, results in clinical consequences [14] while a loss of 15% of TBW is a life-threatening condition.

Dilution methods

From the trivial relationship

$C = N / V$, concentration = number / volume,

any one of these quantities can be determined when two are known. By adding a known number N_{ex} (or a known mass) of an exogenous compound[1], and then measuring the concentration C, we can easily compute the volume V. See Figure 3.

[1] Compounds not existing by natural in the body

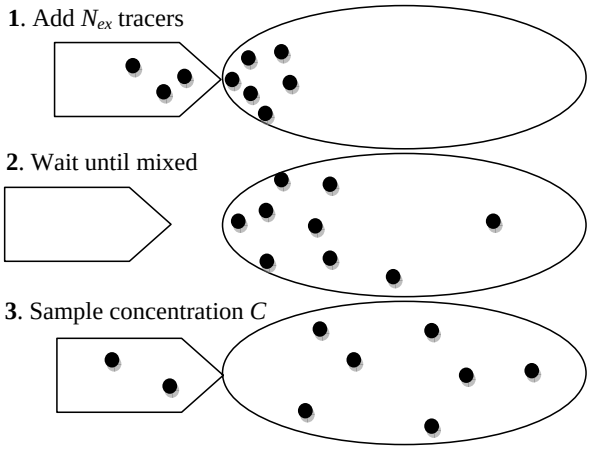


Figure 3. Basic principle of the dilution technique

When adding an endogenous[2] compound, we must first determine the endogenous concentration C_{en}. After mixing, the concentration will be

$$C = \frac{N_{ex} + N_{en}}{V} = \frac{N_{ex}}{V} + C_{en} \rightarrow V = \frac{N_{ex}}{C - C_{en}},$$

where N_{en} is the amount of compound that already resides within the volume V, and

$C_{en} = N_{en}/V$.

Estimating TBW

TBW may be estimated by anthropometric[3] formulae, commonly validated from tracer dilution methods. Anthropometric predictions of various physiological properties may depend

[2] Compounds that already exists in the body – such as glucose
[3] Anthropometry

on height, weight, age, gender, race etc resulting in various degrees agreement of agreement at the level of individuals [15-17]. For example

$$\text{TBW (females)} = -2.097 + 0.1069 \cdot H + 0.2466 \cdot BW,$$

where H is height (cm) and BW is bodyweight (kg). The error could be substantial [17]. This equation does not take into account that the TBW decreases by age [15]. The amount of body fat also influence the TBW: the more fat, the less water [18].

Nevertheless, anthropometric models can be important tools when building models or simulators, in order to verify the coupling to physiology of the model or to explore fluid management *in vitro*[4].

Measuring TBW

The gold standard when measuring TBW is the value determined using isotope dilution techniques, preferable non-radioactive isotopes. The stable water isotopes used are $^{2}H_2O$ and $H_2{}^{18}O$, and the precision can be as high as 1 %, in variation [11, 19]. However, the method used is not clinically feasible due to its complex experimental set-up and the mixing time required for the tracer [20].

Bioelectrical impedance analysis is another method to estimate TBW. By considering the body as a cylindrical isotropic conductor, and applying an electrical signal along the body, it is possible to estimate the amount of water residing within this conductor when considering the composition. However, although simple, quick and cheap to use, there are many sources of error, which may have an impact on the quality of the final result [21].

[4] *In vitro* – experiments outside the body, in an artificial environment. *In vivo* – experiment inside the body.

Intracellular fluid space

The intracellular fluid space (ICF) is the largest fluid space, and has a volume about twice that of the ECF. Although distributed over the 10-100 trillion[5] cells in the human body, each one of which has a unique composition, the ICF is still considered as a single homogenous fluid compartment. The reason for this is the almost identical properties of the cell membranes among all cells, designed to maintain the osmotic equilibrium between the ICF and the ECF [9].

3.2 EXTRACELLULAR FLUID SPACE

The fluid residing outside cells is commonly referred as being in the extracellular fluid space[6], ECF. This fluid can be found in blood plasma, the interstitial space[7], the gastrointestinal tract[8], the cerebrospinal space[9] and the intraocular space[10]. About 20 % of the body fluid resides in the ECF space [10].

Determining the volume of ECF

There are many tracers that can be used to measure the volume of ECF, the most commonly used of which is the bromide ion. The drawbacks of using bromide as a dilution tracer is that it requires a long mixing time, and that bromide does not distribute equally through the ECF [11, 22].

[5] An estimation of, even in the variation of one billion, the number of cells in the human body is incalculable.
[6] Extracellular fluid space or *compartment* or *volume*
[7] Or the *interstitium*, the space between tissue cells
[8] Colon and the small intestines
[9] Fluid in the brain and the spinal cord
[10] Fluid within the eye

Interstitial fluid

The interstitium consists of a gel-type composition of proteoglycan filaments and collagen fibers. Fluid does not pass easily across this gel, but it still serves as an active and fast transport layer for solutes and water into cells. Transport takes place through diffusion rather than convection [23]. The interstitial matrix also contains rivulets and vesicles of "free fluid". In a normal state, the volume of this free fluid is negligible compared to the interstitium as a whole, but these fluid spaces can become enlarged in oedema [24].

3.3 BLOOD VOLUME

The blood volume consists of two parts, the volume of erythrocytes[11] (ECV) and the volume of plasma (PV). The total blood volume (TBV) is distributed between the systemic circulation[12] and the pulmonary circulation[13]. About 84 % of the blood is contained in the systemic circulation [10].

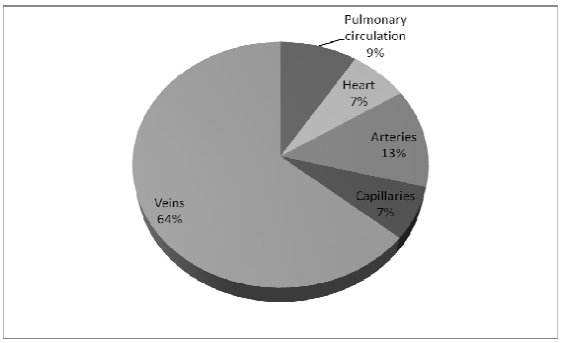


Figure 4. The distribution of blood in the circulation [10]

[11] Red blood cells
[12] The peripheral circulation, to tissues, most of the organs and to the brain
[13] Circulation to and from the lungs

From figure 4, we may see that the veins are the main storage of blood. Even though the capillaries contain a small fraction of the entire blood volume, the cross-sectional area of the capillaries is about 30 – 1000 times larger than the cross-sectional area of any part of the veins or arteries [10].

Prediction of blood volume

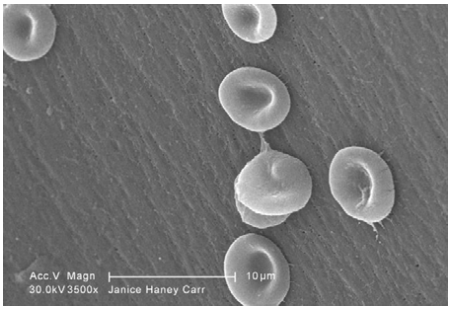
Some anthropometric formulae have been developed through the years. One of those is the empirical formula developed by Nadler et al. [25].

$$TBV\,(Men) = (0.6041 + 0.03219 \cdot BW + 0.3669 \cdot L^3) \cdot 1000$$
$$TBV\,(Women) = (0.1833 + 0.03308 \cdot BW + 0.3561 \cdot L^3) \cdot 1000$$

This formula is extensively used as a reference in work II-IV.

Erythrocytes and Haemoglobin

Each erythrocyte cell in the human body, contains around 300 million molecules of *haemoglobin*. The molecule itself is formed by polypeptide chains, *the globulins*. When synthesized by the ribosomes, they form the haemoglobin chain in which four of those bind together into the haemoglobin molecule (Hb). These four substructures contain an iron atom that is capable to bind one oxygen molecule. Thus, one erythrocyte cell, in theory, may transport over a billion oxygen molecules at the same time [10].



Erythrocytes as scanned by an electron micrograph [26]

The hematocrit

An important parameter is the erythrocyte volume fraction (EVF) of the blood, more commonly known as *hematocrit* (Hct). This parameter is historically determined by packing red blood cells through centrifugation, which separates the red blood cells from the blood plasma, see Figure 5. In a modern clinical laboratory, however, the Hct is measured by other methods[14]. The normal value ranges from 30 % - 50 %.

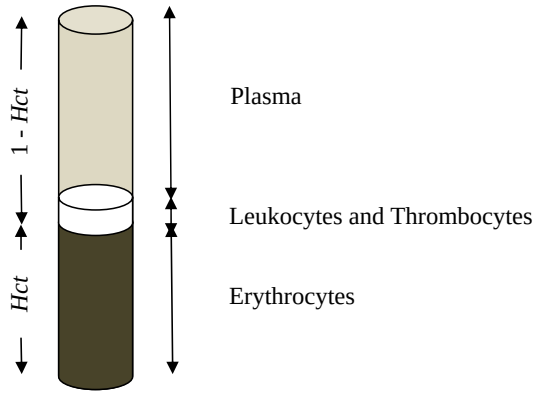


Figure 5. Separation of plasma, erythrocytes and white blood cells. The fraction of erythrocytes in the sample tube is the Hct.

The Hct fraction is extensively used when estimating fluid status, plasma content versus erythrocytes. Though, there is a consensus, that the estimated Hct from lab is overestimated due to trapped plasma[15] [27]. Experimentally determined Hct values, therefore, are sometimes corrected by 0.9 before being used in models, as discussed in paper II [2].

[14] Impedance plethysmography.
[15] Trapped plasma – plasma fluid between packed erythrocytes.

Measuring ECV and PV

The volume of erythrocytes (ECV) may be determined by isotope-labeling erythrocytes with ^{51}Cr and ^{99m}Tc for example [28] but there are other non-radioactive methods, such as labelling erythrocytes with sodium fluorescein [29].

The plasma volume (PV) may be determined by isotope-labeled albumin. The drawback of this method, besides the radioactivity, is that albumin leaks through the capillaries into the interstitial fluid, which gives an overestimation of the distribution volume. The isotope used to mark albumin is ^{125}I. The precision is said to be 3 % [30]. Other commonly used agents are *Evans Blue*, a dye that binds to albumin , and *indocyanine green* (ICG), a dye that binds to globulin [31]. The advantage of these methods is that they are non-radioactive, although the do suffer from other drawbacks. Still, the precision may be as high as that obtained using ^{125}I [20].

If either ECV or PV is known, the other may be computed from Hct by the relationship

$$HCT = \frac{ECV + PV}{ECV}.$$

In Paper I [1], ICG was used initially to measure the plasma volume. Unfortunately, ICG is difficult to obtain, and stocks of ICG in the US were empty at the time, something that illustrates the problem of measuring the plasma volume by this method.

Hb as a diluting tracer

In paper II, we investigated the use of haemoglobin as a tracer and compared Hb concentrations in venous samples with arterial Hb concentration during a crystalloid infusion. Haemoglobin should be ideal as a tracer when estimating blood volume, because of its incapability to penetrate the capillary wall.

Let us start by the relation

$X_{Hb} = V_B \cdot C_{Hb}$,

where V_B (ml) is the initial total blood volume and C_{Hb} is the haemoglobin concentration (mmol/ml). Hence, the plasma volume at baseline, V_p (ml) may be computed from the hematocrit level:

$V_p = V_B \cdot (1 - Hct)$.

The plasma volume, as a function of time, $v_p(t)$ can then be obtained from

$$v_p = \frac{X_{Hb}}{C_{Hb}(t)} \cdot \left(1 - Hct(t)\right).$$

Now, if we consider the vascular volume V_B, to be a completely closed space, we can easily compute the plasma volume by infusing a known amount V_i of crystalloid solution.

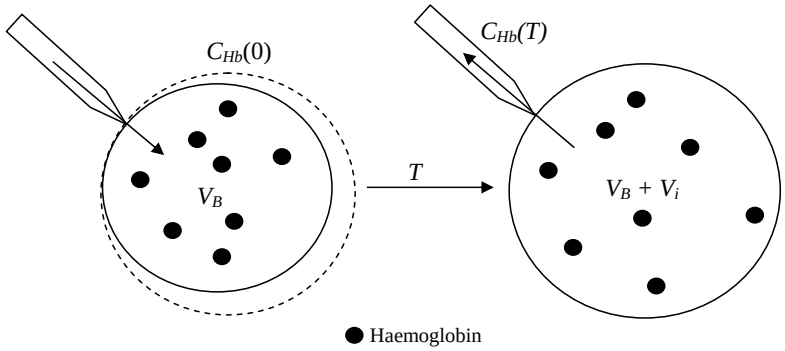


Figure 6. Infusion of fluid into a closed space with the volume V_B and concentration C_{Hb} at $t = 0$. After the infusion and mixing time, at time $t = T$, we measure the concentration $C_{Hb}(T)$.

In this trivial case, the plasma volume is given by

$$V_p = V_i \cdot \frac{\left(1 - Hct(0)\right)}{\left(\frac{C_{Hb}(0)}{C_{Hb}(T)} - 1\right)}.$$

3.4 FLUID BALANCE

Body fluid content

The body fluids contain a wide range of solutes: proteins, glucose and ions – a chemical soup forming a delicate balance regarding acid-base levels and osmotic relationships. This balance is called the fluid *homeostasis* the concept of the *milieu interieur* that was created by Claude Bernard (1813 – 1878) [5]. In presence of a semi-permeable membrane[16], a pressure will arise if there is an osmotic gradient through the membrane. The substances in the different compartments are illustrated in Table 1.

Substance	**Plasma**	**Interstitial**	**Intracellular**
Na^+	143.0	140.0	14.0
K^+	4.2	4.0	140.0
Cl^-	108.0	108.0	4.0
HCO_3^-	24.0	28.3	10.0
Glucose	5.6	5.6	0
Urea	4.0	4.0	4.0
Others	14.0	11.9	130.2
Total mOsm/litre	302.8	301.8	302.2
O_A	282.5	281.3	281.3

Table 1. The constituents of the body fluids (mOsm/litre). O_A is the corrected osmolar activity (mOsm/litre).

[16] A membrane permeable to only some solutes and water, which separates the non-permeable solutes from each other

The final osmolar activity O_A, depends on each substance. This osmolar correction arises when electrostatic forces from dissolved ions are present, which may lower or raise the osmolar activity for a specific solute. The potential osmotic pressure is given by

$$\Pi = O_A \cdot RT ,$$

where R is the gas constant (0.062364 L mmHg K^{-1} $mmol^{-1}$) and T the absolute temperature.

The osmotic balance plays an important role in the fluid distribution, especially between ICF and ECF, and in the filtration process along the capillary bed. The capillary walls are permeable for most of the solutes in the plasma, but larger proteins, such as albumin, do not easily penetrate the membranes into the interstitial space. Thus, an osmotic gradient will be present between the plasma and the interstitium. This potential, or the *oncotic pressure*, exerted by a specific protein *X*, is given by

$$\Delta\Pi(\text{Prot}_X) = \sigma_X \cdot RT \cdot \left(\text{Prot}_{X,p} - \text{Prot}_{X,I}\right),$$

where σ_X is the reflection coefficient for the specific protein combined with the semi-permeable membrane, and $Prot_{X,p}$ and $Prot_{X,I}$ are the osmolar content in plasma and interstitium respectively (mOsm/litre). The reflection coefficient is typically dependant on the size of the molecule: the larger molecule, the larger the σ_X and the lesser size of pores of the membrane, the larger the reflection coefficient [10].

In Paper I, we used the relationship between oncotic gradients and hydrostatic pressure to quantify changes of the filtration process during bleeding. The Starling equation states that the filtration flow J_v is given by

$$J_v = k \cdot \left(\sigma \cdot \left(\Pi_p - \Pi_I\right) - \left(P_p - P_I\right)\right),$$

where P is the hydrostatic pressure in the capillaries (P_p) and the interstitium (P_I) (mmHg), and k is a fluid filtration coefficient, sometimes referred as the *capillary hydraulic conductivity* [32].

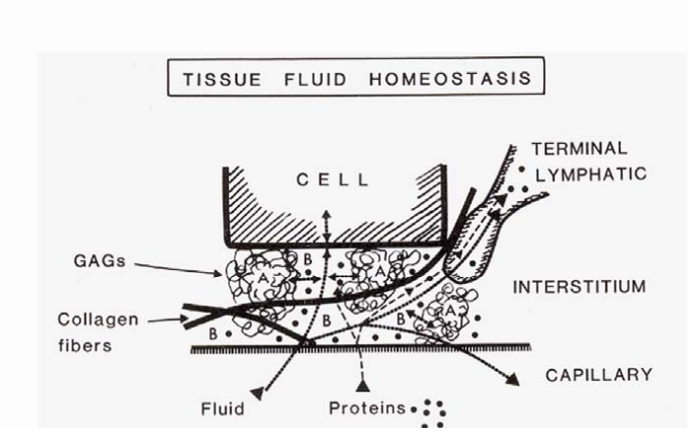


Figure 7. Schematic diagram of the interstitium. From the capillaries below, fluid filters through the capillary wall and enters the interstitial gel. Solutes and fluid are exchanged with cells, and any superfluous fluid and proteins are pumped away through the terminal lymphatic. *Lymphology 11:128-132, 1978.* Permission from the author.

Fluid feed-back system

The balance of salt and water, is governed by a complex feedback system that involves hormones: ADH (antidiuretic hormone), RAS (renin-angiotensin), ANP (atriopeptin), ALD (aldosterone), ANG II (angiotensin II) and specialised cell receptors; baroreceptors and osmoreceptors, see Figure 8.

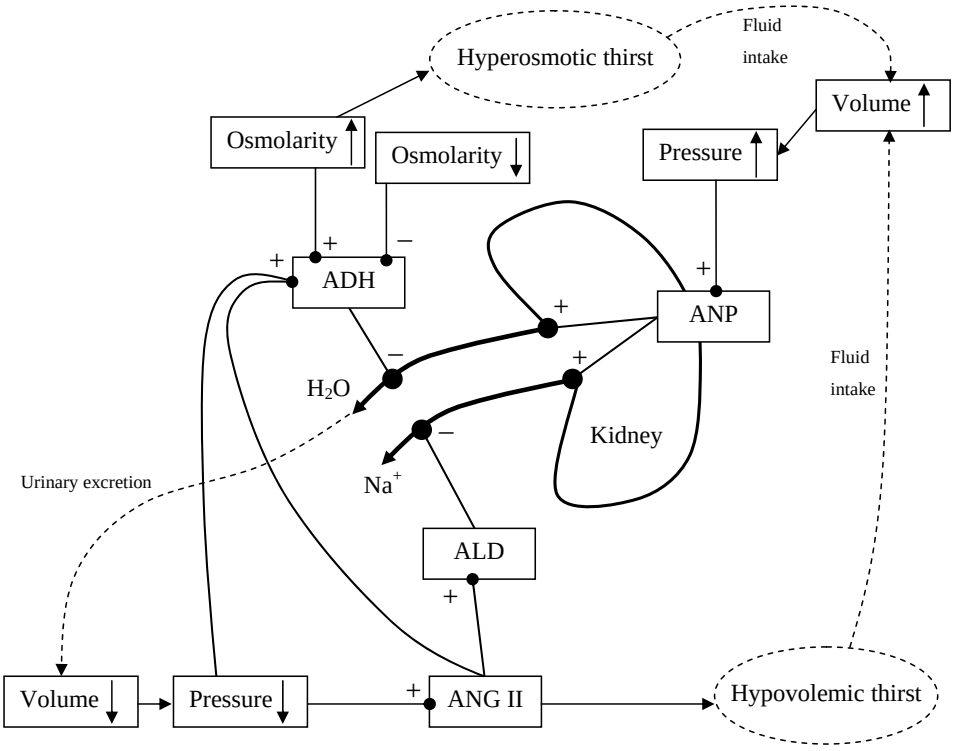


Figure 8. Overview of salt and water regulation, cf. [33]

3.5 CIRCULATION AND FILTRATION OF BODY FLUIDS

Until 1628, the liver was thought to be as an inexhaustible reservoir of blood. In the liver, food was transformed into blood, which then streamed into the right side of the heart where it was heated and then pumped out to the limbs where it was consumed. Considering our knowledge today, producing 5 litres of blood per minute, would be a quite remarkable exploit by a single organ. However, William Harvey took one step forward in mankind's understanding of the blood through his dissertation *De Motu Cordis* [34]. He could not, however, explain how the blood passes from the arteries to the veins. It was not until the invention of the microscope that the existence of the capillaries and their function was understood [20].

Blood pressure control

The blood pressure is controlled by either *parasympathetic stimulation*[17] or *sympathetic stimulation*[18], which adjust oxygen delivery and the distribution of fluid between the different fluid compartments.

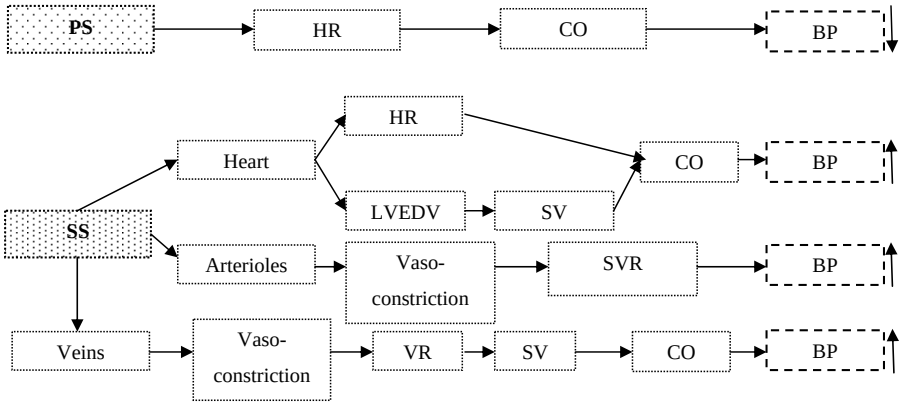


Figure 9. The parasympathetic (PS) and the sympathetic stimulation (SS) of blood pressure (BP). Through regulation of heart rate (HR), cardiac output (CO), stroke volume (SV), venous return, systemic vascular resistance (SVR) and left ventricular diastolic volume (LVEDV).

The pressure/flow relation in the human body is given by, using the abbreviations from Figure 9,

$$BP = CO \cdot SVR = (SV \cdot HR) \cdot SVR.$$

BP is also referred as *mean arterial pressure*, *MAP*, computed as

$$MAP = \frac{2 \cdot DP + SP}{3},$$

[17] The activity of the nervous system during rest
[18] The activity of the nervous system during stress

where *SP* is the systolic blood pressure and *DP* is the diastolic blood pressure. The systolic pressure is the maximum arterial pressure reached during the heart's systolic phase – "the pump out". The pressure then drops to the diastolic pressure, before being raised again. See Figure 10.

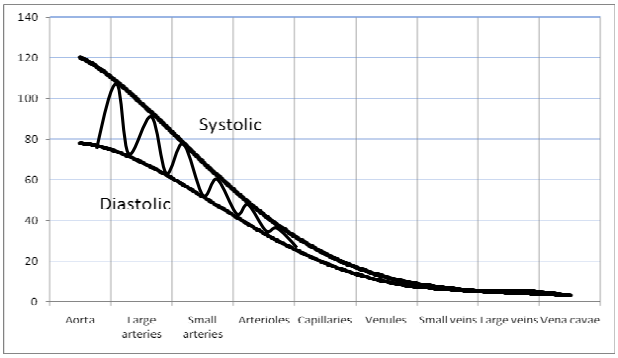


Figure 10. Principal sketch over the pressure fall (mmHg) through the systemic circulation, cf. [10]

Macro-circulation

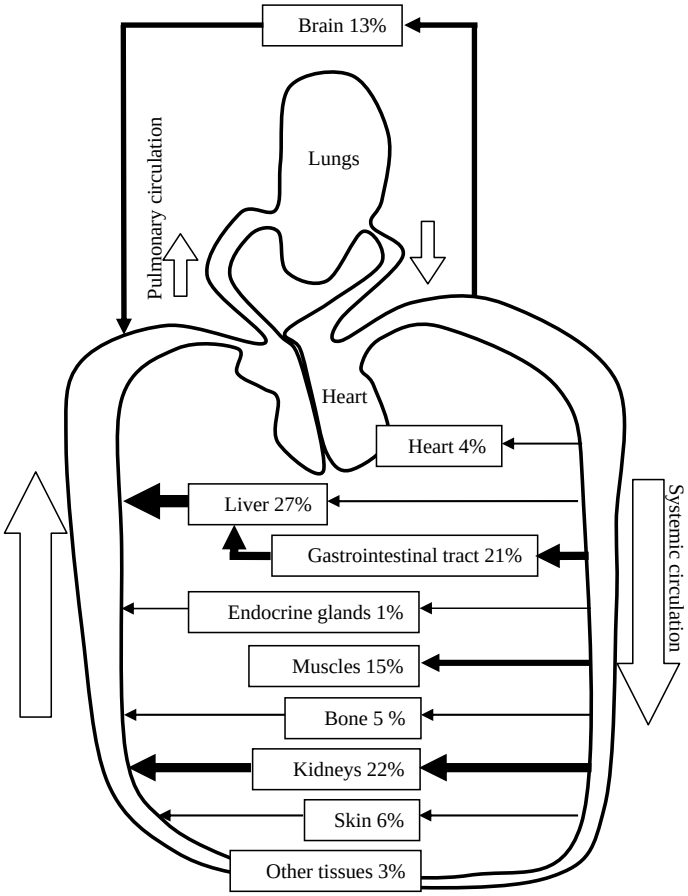


Figure 11. Overview of the circulation and the distribution of cardiac output over various organs during rest, cf. [10].

Micro-circulation

The micro-circulation, or *microvascular fluid exchange*, takes place in the capillary bed, where the exchange of nutrients, blood gases and water takes place. See Figure 12.

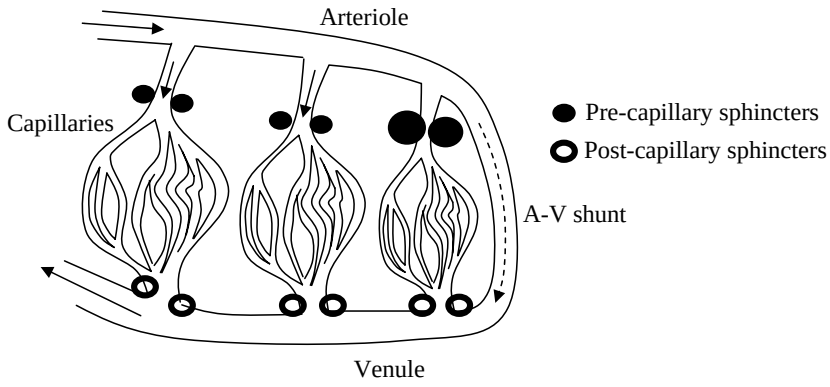


Figure 12. Sketch of the microcirculation through the capillary bed. The inflow of blood (solid arrows) into the capillaries is controlled by the sphincters. The blood may bypass the capillaries through a shunt (dashed line).

Figure 12 shows the role of the pre-capillary sphincters. By controlling these smooth muscles, the inflow into the capillaries may be adjusted and even cut-off completely. Post capillary sphincters work in close relationship with pre capillary sphincters. Paper II refers to A-V shunts, through which blood passes the capillary bed, when the pre-capillary sphincters are closed.

The property of the capillaries, and their filtrating abilities, differ vastly between organs and tissue. As an example, the reflection coefficient of albumin in different regions varies from 0 (spleen), 0.9 (skeletal muscle) to 1.0 (brain) [20].

Thus, in general, the behaviour of the capillary wall, which is, as discussed earlier, a semi-permeable membrane, is governed by micropores. These are usually divided into three categories – aquaporins, small interendothelial pores and large pores [35]. The large pores are permeable to all solutes. These are less frequent than the small pores, but may arise when the

capillary wall is disrupted due to inflammation or other pathological states. The aquaporins are permeable only to water.

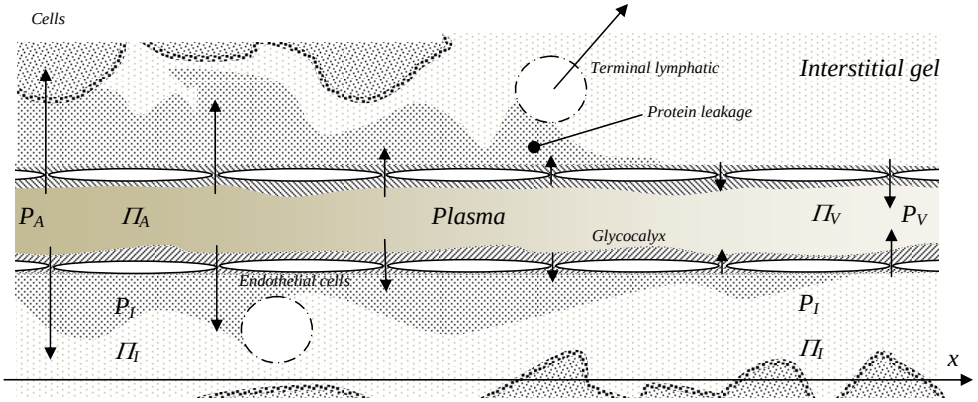


Figure 13. The capillary process over a distance *x* through the capillaries. Solutes, water and proteins diffuses through the small pores between the endothelial cells.

Figure 13 shows the basic principles of filtration. The blood flows from left to right, due to the pressure gradient $P_A - P_V$. Water and small solutes tunnel through the small pores and diffuse through the interstitial gel. However, amounts of some proteins, such as albumin, leak through the small pores. Eventually, any excess water, superfluous proteins and other solvents are pumped away through the lymphatic ducts. The net filtration ΔJ of *one* capillary route may be computed from:

$$\Delta J = \int_A^V k \cdot \left(\sigma \cdot \left(\Pi_p(x) - \Pi_I(x)\right) - \left(P_p(x) - P_I(x)\right)\right) dx \,.$$

The interstitial hydrostatic and oncotic pressure is sometimes considered to be constant through the capillaries when modelling the phenomena [36].

The total net filtration of the body (estimated to 2 ml/min [10]) is eventually transported back through the lymphatic ducts into the veins.

4 CLINICAL PERSPECTIVES

Jean Baptiste Denis (1620 – 1704)
The first successful blood transfusion 1667

4.1 INTRODUCTION

The knowledge of the necessity of an adequate circulation is probably as old as mankind. The first successful transfusion of blood is said to have been carried out 1667, when a physician, infused blood from sheep to a hypovolemic man. Naturally, only a few of these treatments were successful, which forced the Royal Society of London, the French Parliament and the Church of Rome to prohibit further experiments. Not until the end of 19th century did blood

transfusion and fluid infusion become increasingly safer due to awareness of the blood constituents, the capillary mechanisms and the need of sterile equipment [20].

An adequate circulation and fluid homeostasis is of a critical importance in a wide range of clinical applications, especially during surgery. Virtually all surgical patients receive intravenously administered fluid during their hospital stay [20].

4.2 DEHYDRATION

Symptoms

Early symptoms of dehydration include a dry mouth, low urinary output, absence of tears, tiredness, sunken eyes, dark and concentrated urine and markedly increased skin turgor [38].

Other more severe symptoms will arise due to electrolyte imbalances, an impaired perfusion of important organs and impaired cardiovascular capabilities. These symptoms may be non-specific – weakness, dizziness, fatigue, chest pain, confusion or muscle cramps. If the dehydration gets worse, the condition may lead to hypovolemic shock, organ failure and ultimately death [39].

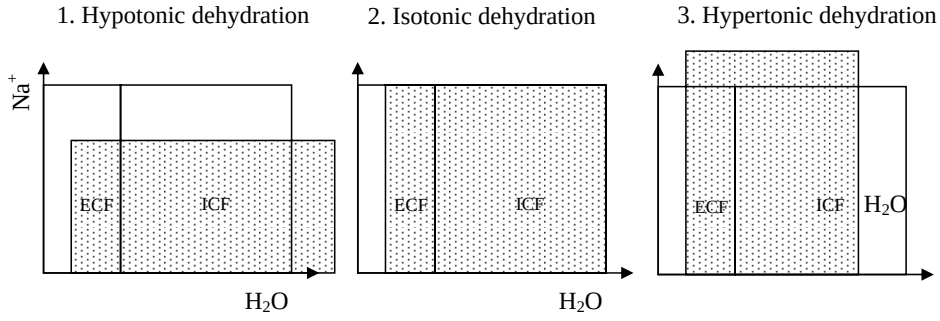


Figure 14. Three common states of dehydration. Salt and water move from the optimal homeostasis of ECF and ICF into a dehydrated state (dotted areas).

Figure 14 shows three different stages in dehydration are exemplified. Dehydration may arise from several pathological states including diarrhea, impaired renal function, reduced sensation of thirst, and fever.

Children

The daily turnover of TBW for an average adult, as previously stated, was about 5-10 % of TBW which corresponds to 35-70 ml/kg and day. The turnover rate is higher in infants: 160 ml/kg and day (3 months), 100 ml/kg and day (12 months) and 65 ml/kg (3 years) and day [40]. Because of the renal and cardiovascular immaturity in infants, and the higher turnover, the body fluid homeostasis is much more critical for paediatric patients than it is for adults [41]. Thus, dehydration of infants is an acute syndrome that has to be treated immediately.

Elderly

Dehydration is a significant problem for the elderly population as the body composition of water changes with age towards a drier state [16]. This physiology in combination with slight hypoaldosteronism[19], reduced sensation of thirst, impaired ability to concentrate urine and, in many cases, forgetfulness to drink can lead to significant dehydration and a troublesome situation for patients and caregivers. The consequences of dehydration are several and sometimes severe: vertigo and imbalance leading to falls, urinary- and respiratory infections with or without septicaemia[20], delirium, renal failure and increased risk for medication toxicity. Elderly with co-morbidities are at an increased risk for repeated hospitalizations [42-44]. Perhaps the most significant consequence of dehydration is an increased mortality among hospitalized older adults [45].

4.3 HYPERHYDRATION

Hyperhydration may occur due to pathophysiology or an excessive fluid administration. If the capillary filtration increases, due to increased hydrostatic capillary pressure or an increased

[19] Decreased levels of the hormone aldosterone
[20] Systemic inflammatory response syndrome (SIRS) or blood poisining

permeability of the capillary walls, the lymphatic system may not be able to remove excess fluid.

This situation may arise during congestive heart failure, where the venous return is poor or as a result of lowered muscular activity (due to hospitalization for example), which is needed for the lymphatic drainage to work adequately. Other pathophysiological causes are kidney failure (which causes water retention), famine, burns, septicaemia etc., all of which are conditions that may increase the local filtration rate and re-absorption in the capillaries.

Eventually, overhydration leads to peripheral oedemas; and in worst cases: pulmonary oedemas, which is a life-threatening condition [46].

Symptoms vary and include anxiety, confusion, headache and nausea may as a result of excess fluid exerting a higher pressure on the brain.

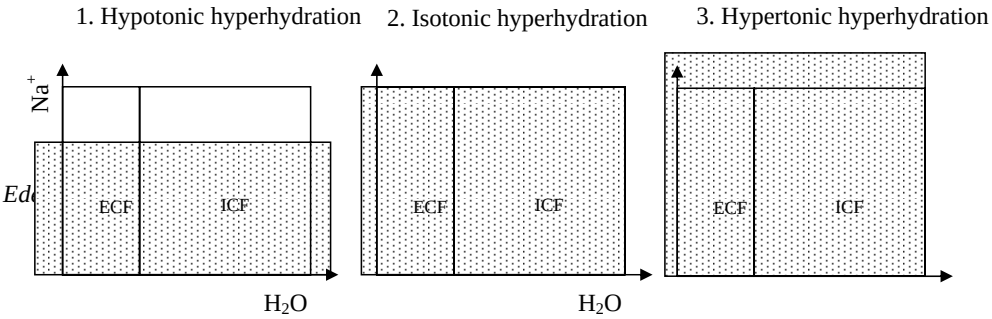


Figure 15. Three stages of hyperhydration [47]

Figure 15 shows the main pathophysiological states of hyperhydration.

4.4 BLEEDING

Loss of blood volume due to bleeding stimulates virtually the same process of defending the volume as dehydration does. Symptoms of bleeding include decreased blood pressure,

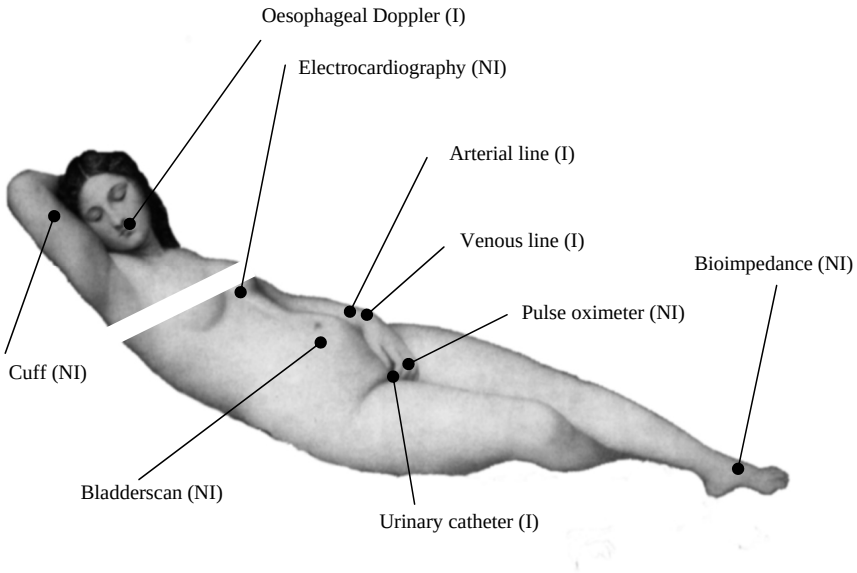
increased heart rate, reduced urinary output, pallor with cold sweat and thirst [33]. This state is called *hemorrhagic shock*.

Several important responses, including hormonal responses, which eventually restore the circulating volume, are stimulated. The volume, however, can only be restored if the bleeding is stopped.

Firstly, the filtration decreases when the capillary hydrostatic pressure decreases, leading to a fast drainage of protein-free fluid from the interstitium to the plasma volume. As much as 75% of the blood volume loss is restored due to this effect within an hour [48].

We show in Paper I that this effect is significantly reduced during isoflurane anaesthesia. The starling equation enabled us to quantify this effect by separating the mean hydrostatic capillary pressure and the mean oncotic effect of transcapillary refill.

5 MATERIALS AND METHODS



Common sampling sites of clinical outputs relevant to assess hydration and hemodynamical status. I - Invasive[21] and NI – Non-invasive. *From "Sleeping Venus" by the Italian painter Giorgone (1477-1510).*

In this section I will go through the materials and methods used in this thesis. In Table 2 we have listed some of the methods.

[21] Invasive – within the body

	Parameters	**Time to result**
Arterial/Venous line	Glucose, Hb, Hct, pH, hormones, ions,…	1 min – *several hours*
Electrocardiography	Heart variability, heart rate	< 1 min
Bladderscan	Urine volume	< 1 min
Cuff	Blood pressure	< 1 min
Oesophageal Doppler	Cardiac output index	< 10 min
Pulse oximeter	Oxygenation	< 1 min
Bioimpedance	Total body water	< 10 min
Urinary catheter	Urine output, urine content	1 min – *several hours*

Table 2. Clinical output of various parameters.

Hemodynamics

Hemodynamical parameters include mean arterial pressure, MAP (mmHg) and cardiac output, CO (L/min).

Paper I

At 5-min intervals, heart rate, MAP, right atrial pressure, mean pulmonary arterial pressure, and the pulmonary arterial occlusion pressure (PAOP) were measured using a Hewlett Packard 78304 (Santa Clara, CA). Cardiac output was measured in duplicate using iced saline thermodilution (Cardiac Output Computer, Baxter, Irvine, CA).

Paper II

Monitoring consisted of electrocardiography (ECG), pulse oximetry and noninvasive arterial blood pressure measurements (Cuff).

Paper III

Hemodynamic supervision was maintained by electrocardiography, pulsoximetry and non invasive blood pressure measurements (Cuff) (Propaq 104, Systems Inc., Beaverton, OR).

Paper IV

The blood pressure was monitored by a non invasive digital blood pressure monitor (Omron®, Kyoto, Japan) at time points 0, 15 and 120 minutes, through a cuff.

Blood

Blood properties include haemoglobin concentration, Hb (g/dL), plasma volume, PV (ml), hematocrit, Hct and red cell count, RBC.

Paper 1

Hct and Hb were measured using 1-ml arterial samples (HemaVet 850, CDC Technologies, Oxford, CT). PV at baseline was measured using indocyanine green (ICG; Akorn Inc., Buffalo Grove, IL).

Paper II

Cannulae were inserted into one radial artery and the antecubital veins in both arms. The arm with both arterial and venous access was used for blood sampling and the other side for the infusion of fluid. Arterial and venous blood were simultaneously sampled at precisely timed intervals for analysis of Hb and Hct, using a Technicon H2 (Bayer, Tarrytown, NY) which determines Hb by colorimetry at 546 nm.

Paper III

Intravenous cannulas were placed in antecubital veins on each side. One cannula was used for blood sampling, the other for fluid infusion. Blood samples (4 mls) were taken every five minutes during the first 120 min, and thereafter the sampling rate was every 10 min until the end of the experiment at 240 min. Hb and RBC were analyzed using a Coulter Counter STKS device (Coulter Electronics, Hialeah, FL, USA).

Paper IV

Blood samples were taken at time points 0, 10, 15, 20, 30, 45, 60, 75, 90, 120 minutes. Total study time was two hours. Haemoglobin and haematocrit were measured by fluorescent flow cytometry (XE-5000, SYSMEX, Stockholm, Sweden).

Urine

Paper I

One day before each experiment a urinary bladder catheter was inserted into the sheep (Sherwood Medical, St. Louis, MO). Urinary volumes were measured every 5 min.

Paper III

A standard bladder catheter, connected to a drip counter to monitor urine excretion continuously, was inserted before the experiment (Sherwood Medical, St Louis, MO).

Paper IV

The urinary bladder was scanned at 0, 15 and 120 min by an ultrasonic scanner BVI-3000 (Bladderscan®, Allytec, Stockholm, Sweden). The volunteers were allowed to void during the

experiments. The amount of voided urine was estimated. At the end of the experiments the patients were once again weighed before and after voiding.

Plasma content

Plasma content includes glucose (mmol/ml) and total plasma protein, Prot (g(dL).

Paper I

Blood was withdrawn every hour for measurements of Prot by refractometry (Shuco, Tokyo, Japan) and of serum colloid osmotic pressure (4100 Colloid Osmometer, Wescor, Logan, UT).

Paper IV

Glucose concentration was analyzed by a photometrical method (Roche Diagnostics, Modular P-800, Indianapolis, USA).

6 FLUID THERAPY

A desert tree in Tenerife, Canary Islands [37]

6.1 INTRODUCTION

What exactly do we mean when we talk about fluid therapy? If we consider a plant, we know more or less instinctively that if we supply too little water, the plant will dry out and finally die (restricted diet). If we supply too much, the plant may drown and ultimately die (generous diet). However, we also know that a plant does not need an exact amount of water every day. We just pour some water regularly onto the plant and it seems to adapt to our care-giving. As long as it survives, we conclude that we are doing the right thing. Would a patient in intensive care for example, accept this fluid strategy?

The fluid balance in the human body is much more than considering the turnover of water, of course, and by far more complex than any fluid therapy of plants, restricted or generous. It is

also a matter of fluid content; ions, proteins, glucose etc that has to be “in balance” - the fluid *homeostasis*.

Our body can compensate disturbances, by either adapting to this new “balance” or by other mechanisms that suppress the perturbation.

What is the optimal fluid balance for an individual? Is it possible for a clinician to determine by a simple method a fluid strategy to obtain this optimum for any individual patient? And what are the end-points that the clinician should aim at?

6.2 THE FLUIDS

Crystalloid fluids

Crystalloid fluids are solutions of small particles, containing both ions and non-ions. The colloid pressure contribution is zero, and such fluids thus contain only solutes that pass freely through the capillary membrane.

In paper II, we used *lactated* Ringer’s solution (ionic content: Na^+ 130 mM, Cl^- 109 mM, Ca^{++} 3 mM, K^+ 4 mM, acetate: 28 mM, pH 6.5, osmolality: 273 mOsm/l).

In paper III, we used *acetated* Ringer’s solution, 25 ml/kg (ionic content: Na^+ 130 mM, Cl^- 110 mM, Ca^{++} 2 mM, K^+ 4 mM, lactate: 30 mM, pH 6, osmolality: 270 mOsm/litre).

These solutions contain lactated or acetated ions for pH-buffering reasons. They are mildly hypotonic. Since acetate may be metabolized by all cells, in contrast to lactate which can be metabolized only in the kidney and liver, it might be more beneficial to use acetate in situations with poor circulation. However, no clinical study has yet showed any significant clinical difference between the solutions in a clinical setting [49].

Colloid fluids

Colloid fluids contain solutes that lead to an increase in oncotic pressure. They are mainly used for replacing lost blood and for goal directed protocols, and the risk of forming oedema is lower than it is when using crystalloid fluids, since they tend to allocate intravascularly. However, if there is a pathological situation with increased capillary leak, colloids might contribute even more to the formation of oedema. Furthermore, there is a trade off between replacing lost intravascular volume and overload of the circular system which might have detrimental effects on patients with cardiac failure. Colloids are also expensive and in major randomized clinical trials there are no differences in outcome between crystalloids and colloids [50-51].

There are four main groups of colloid fluids; albumin solutions, starches, dextrans and gelatins.

Colloids in general, are more expensive than crystalloids, and the most expensive colloid is the albumin solution [52]. The synthetic colloids can induce anaphylactoid reactions. Starches and dextrans may alter coagulation and renal function [20]. Dextrans may even cause severe anaphylactic reactions which can be prevented by giving low molecular sized dextran-1[22] [53].

Hypertonic fluids

Combined solutions of hypertonic crystalloids and colloids are extensively used in several clinical settings [20].

Hypertonic solutions, like colloid solutions, are mainly used to restore the plasma volume. Moreover, the hypertonic solution also promote urine output [54], increase of cardiac contractility and vasodilatation of the peripheral vasculature [55].

[22] A solute containing small colloids (hapten), given some minutes before infusion of dextran to prevent the anaphylactic reaction.

However, hypertonic solutions with or without a colloid may cause some adverse effects such as hypernatremia, but the high level of sodium is transient. One major concern however, is if these solutions are given too rapidly, they may worsen an acute bleeding in a trauma situation [56]. However, they might have anti inflammatory properties that might be beneficial.

Glucose solutions

Glucose solutions, as used in Paper IV, are commonly used, especially during surgery of hypoglycaemic patients. Furthermore, infusion of a glucose solution provides an energy store that may benefit patients undergoing thoracic surgery. These solutions are also used post-operatively and during post surgical rehabilitation in the ward.

6.3 PER-OPERATIVE FLUID STRATEGY

Fluid management is an important part of per-operative care, as a tool to keep patients stable regarding the circulation, oxygen delivery, organ perfusion, acid-base balance and the overall fluid homeostasis.

Thus, the clinician will aim at some important end-points during per-operative fluid management:

1. The organs and tissues should be well perfused, especially vital organs such as the heart, liver, brain and kidneys
2. The blood volume should at least remain at baseline
3. Cardiac output should be optimal
4. Blood pressure should be kept stable
5. Urine output should be relevant in comparison to the fluid balance
6. Oxygen delivery and consumption should be optimised

These end-points are commonly used in a conventional approach to per-operative fluid therapy based on visible clinical signs and laboratory values. Due to the high level of

complexity of the circulation system, the clinician is referred to endpoints such as measurement of blood pressure, urinary output and heart rate but would probably be better off if clinical decisions could be based on a more accurate understanding of the underlying fluid balance [20].

Furthermore, the final therapy will depend on the pathophysiology and type of surgery. Heart failure patients [57], severely burned patients [58] or neurosurgical patients [59], for example, may require that other considerations overrule the conventional approach.

6.4 OPTIMIZING CARDIAC OUTPUT

If cardiac output (CO) is monitored, by an oesophageal Doppler for example, the goal directed fluid strategy aims to increase the cardiac filling until the heart muscle does not respond with increased work any longer. This limit is hypothetical and based on the assumption that an intravenous volume load will increase the filling of the heart, which then increases cardiac output (Starling forces). If a patient receives fluid, and *CO* increases, then this patient is a “responder” – he or she responds adequate to the fluid infusion. If the patient does not respond to the load, then the patient is considered to already be optimized and a “non-responder” [60-62].

A non-responder may increase the cardiac filling due to an intravenous fluid infusion; however, the heart will no longer be able to pump out the fluid in the same rate. In this situation, any more administrated fluid is superfluous, and will eventually cause cardiac failure with subsequent interstitium oedemas.

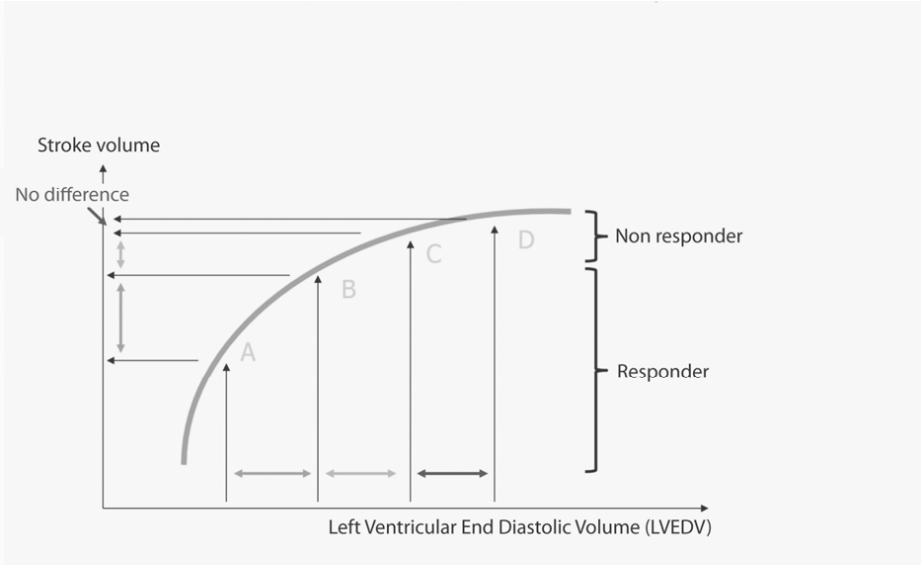
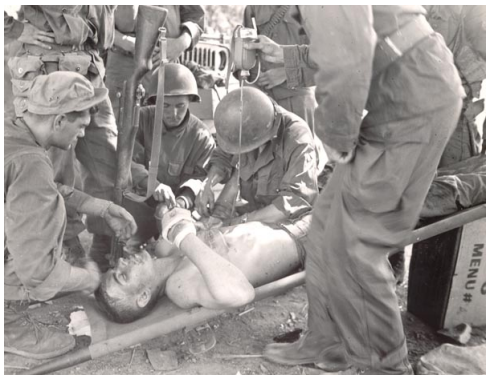


Figure 16. Illustration of a goal-directed fluid administration, when CO (= SV · HR) and cardiac filling (LVEDV) are monitored. In this example, the two first infusions A and B shows a response while C and D no longer give any response [62].

6.5 ADVERSE EFFECTS OF FLUID THERAPY

Regardless of what endpoint is chosen for per-operative fluid management there is an inevitable movement of protein-free fluid to peripheral, functional or non-functional parts of the body at least when using crystalloids.

Clinicians observed a phenomenon in the army hospitals at Da Nang during the Vietnam war: “wet lung syndrome” or the “Da Nang lung”. This was due to a new fluid regimen, used to treat patients suffering from trauma, in which an exaggerated use of crystalloids was used, together with packed red blood cells.



1st Lt. Francis Curtin, Bellingham, Washington, MC, gives plasma to an unidentified wounded American soldier somewhere in Korea. 7 Aug 1950. *From The Office of Medical History, U.S. Army Medical Department and Army Medical Command.*

This new treatment showed a better outcome than the fluid regimen used in the Korean War, where the extensive use of colloids and plasma sometimes resulted in renal failure [63]. Thus, the large amounts of crystalloids prevented renal failure in Vietnam, but instead caused pulmonary oedema, later understood to be caused by *Acute respiratory distress syndrome* (ARDS) [64]. The improved survival rate in Vietnam could, however, could have been attributed to better field care, rapid evacuation and early surgical stabilisation and not the fluid treatment *per se*.

The fluid resuscitation strategy from Vietnam, originally based on ideas of Shires et al. [65] later found its way to civilian practice, which meant that practitioners started to give large amounts of crystalloids to ordinary elective surgical cases in the ORs[23] [66].

Peripheral upload of fluid

Fluid shifting out of the vasculature is still an apparent problem during anaesthesia and surgery. This occurs intra-operatively as well as during several days postoperatively.

Due to the nature of the capillary endothelial wall it is inevitable that protein-poor fluid will move to interstitial tissues. Patients can accumulate such fluid extensively, and increase their

[23] Operating rooms

postoperative weight and, increases in morbidity and mortality [67] have been attributed to this increase in weight. These side-effects can be cardiopulmonary complications, slower tissue healing and a general increased hospital stay [6, 68].

Moreover, when the endothelium is damaged, as is the case in septicaemia, the leakage of protein-rich fluid may also increase. There is an overwhelming consensus that excessive peripheral fluid accumulation that causes weight-gain postoperatively is detrimental [69].

Fluid shifting is also particularly exaggerated during pathological conditions and if addressed wrongly by giving large amounts of crystalloids this could be detrimental to the patient [67, 69].

A *rational approach* of fluid therapy was suggested by Chappell et al.[70]. A healthy vascular endothelium is coated by the endothelial glycocalyx, which is considered to play an important role in the filtration process. During infusion, the function of glycocalyx may be altered due to the shear force of infusing fluid. The glycocalyx might be more permeable and allow more fluid to escape to the interstitium.

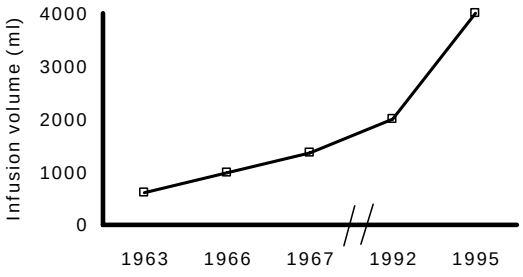


Figure 17. The steadily increase of infusion volume during surgery (here cholecystectomies). By permission of *Kathrine Holte*.

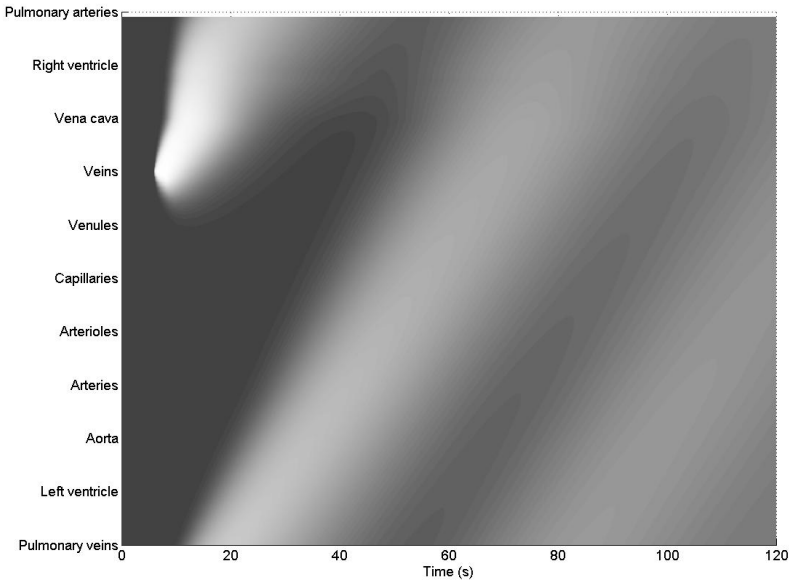
In addition to peripheral accumulation, and the forming of oedemas, fluid therapy may induce several other serious adverse effects if not used properly; hypertension, hyperchloremic

acidosis and renal failure are some of them [20]. Chappell and co workers suggest a moderate crystalloid fluid replacement in combination with a colloid replacement of lost blood.

Conclusions

Fluid therapy during the last ten years are moving back to protocols according to the original researchers findings in the 1930s – the body strives to maintain salt and water when it is stressed. Consequently, hospitals are abandoning the aggressive crystalloid period and going for more restrictive protocols [6, 70-71].

7 MATHEMATICAL MODELLING OF BODY FLUIDS



The image shows the result of a computation of a dispersion-convection PDE, based on a fractal tree representing the vascular system. A solute is injected in the peripheral veins at t = 3 s, and disperses by diffusion and convection through the cardiovascular tree. This model is based on the work by Dokoumetzidis et al. [72]

7.1 INTRODUCTION

The use of mathematics in describing basic principles of nature plays a fundamental role for mankind when coming to understanding or explaining a certain phenomena predicting future phenomen. Statistics, one of many mathematical disciplines, are extensively used in clinical science. However, other areas such as bioinformatics, pk/pd-modelling, computational genomics, biophysics have been added to the increasing field of science. They are commonly

addressed as the *biomathematical fields*. It is worth mentioning a few mathematical concepts/disciplines within the field of modelling body fluids and fluid therapy.

7.2 OVERVIEW

Compartmental dynamic system (CDS)

In this section I will refer to a several disciplines, using the same concepts, as CDS. A CDS consists of a finite number of units, called *compartments*. The basic compartment contains a finite amount of an *agent*, which is considered to be evenly distributed within the compartment (well-stirred). There may be flows, transporting the agents from or into the compartment, as long as the mass conservation holds for the CDS. A system that is both inflow and outflow-closed is said to be a *closed system*.

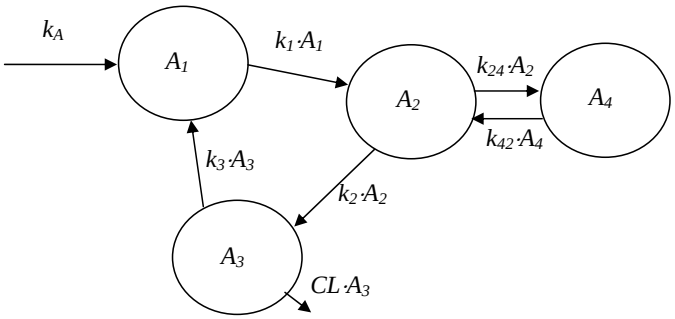


Figure 18. An example of a CDS.

CDC provides an intuitive approach of understanding and analysing otherwise complex dynamical systems and the mathematics is well established (compartmental analysis) [73].

Pharmacokinetics (PK)

The word “Pharmacokinetic” was established by F. H. Dost, a Professor in Germany who defined it as “the science of the quantitative analysis between organisms and drug” [74]. By pharmacokinetic modelling and computation, characteristic properties and the activity of a drug may be quantified in their ability of binding to tissues, proteins, fluids etc, the volume of distribution, half-life of concentration, rate of metabolism, excretion rate and much more [74-75].

Physiologically based pharmacokinetics (PBPK)

The pharmacokinetic concepts may be expanded into physiologic mathematical models, where the drug interacts in relation to blood flows, organs and tissue volumes [76]. This methodology is referred as PBPK.

Lumped element models

Also called *lumped parameter models.* This methodology, in physiological contexts, simplifies hydrodynamics into a CDS model with expandable volumes. Now, flows, fluidity and resistance govern the flows between compartments [77-78]. They are also referred as *electrical analogues,* since they may be transformed in to electrical circuits [79]. They can be further extended also to take into account the dynamics of osmolar content [32].

Computation fluid dynamics

This computational research field, within fluid dynamics, basically deals with the Navier-Stokes equation for arbitrary boundary conditions. These boundaries may represent virtually any part of the body exposed by a flow [80]. Because of the complexity of the mechanisms that governs flow of fluids, the computational effort and the build up of a valid domain, may limit the usefulness for larger regions. Though, there exists simplified models with fluid dynamical elements [36].

Full-body simulators

Some full-body simulator of the body fluid dynamics have been developed during the years for the purpose of education [81] and research [32, 82].

Control concepts

The use of control theory, the mathematical/engineering discipline dealing with dynamical systems, is obvious since a wide range of biological processes, consisting of feedback mechanisms including receptors, hormones and other regulating stimulators may be described as open or closed loop systems. The methodology offers a compact approach of describing such systems with a few set of parameters. This should be compared with the lumped element method, where complex physiological systems virtually need a large number of parameters to correlate with empirical data adequately [83].

7.3 FLUID KINETICS

Fluid kinetics, or *volume* kinetic, analysis is a method to compute body fluid dynamics due to various clinical perturbation of the full body fluid distribution. The advantage of using this fairly simplistic approach, of an otherwise complex physiological mechanism, is that only one tracer is needed – haemoglobin.

By using linear models, we may quantify the full-body volume effect of fluid administration through a finite set of parameters. Compared to pharmacokinetics, fluid kinetics examines the *volume effect* of various fluids.

The basics

Fluid is administrated either intravenously by k_i [ml/min] or per orally by k_o [ml/min]. In the latter case, the fluid must pass an intermediate compartment V_o before entering the central fluid space V_1. V_1 [ml] is the estimated initial distribution volume of haemoglobin which have the quantity X_{Hb} [mmol]. From V_1, the fluid is eliminated by the rate constant k_r [ml/min] and by the basal elimination k_b [ml/min]. Furthermore, V_1 is communicating with the peripheral fluid space V_2 by the parameter k_t. In the presence of osmotic gradients between the cellular and interstitial fluid space, water is exchanged by the rate k_c [ml/min].

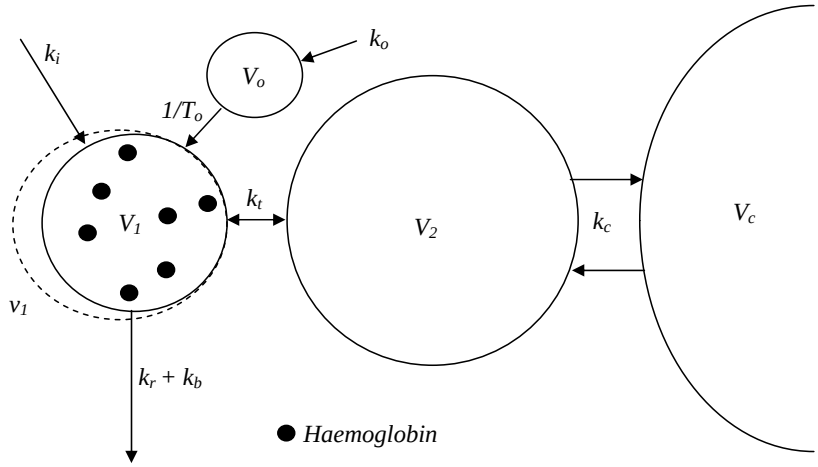


Figure 19. Kinetic pathway of fluid

In fluid kinetics, we make use of *dilution* rather than *concentration.* The relative change, or the dilution, is dimensionless and defined as:

$$\frac{v_p - V_p}{V_p} = a\lg ebra = \frac{C_{Hb}(0)\cdot\left(1-HCT(t)\right)}{C_{Hb}(t)\cdot\left(1-HCT(0)\right)} - 1 = dilv_1$$

Assuming $v_p = v_1$, and disregarding any osmotic imbalances, the kinetic equations sums up into a system of ordinary differential equations:

$$\frac{dv_1}{dt} = k_i(t) - k_t \cdot \left(dilv_1 - dilv_2\right) - \frac{dU}{dt}$$
$$\frac{dv_2}{dt} = k_t \cdot \left(dilv_1 - dilv_2\right)$$
$$\frac{dU}{dt} = k_r \cdot dilv_1 + k_b$$

the two volume model with intravenous administration of isotonic fluid. The parameters k_t, V_1, V_2, k_r and k_b are estimated by nonlinear minimization routines after solving the system either analytically or numerically.

Amount model

By substituting $v_1 - V_1$ by a_1 and $v_2 - V_2$ by a_2, we may rewrite the differential equations as:

$$\frac{da_1}{dt} = k_i(t) - k_{t,1}a_1 + k_{t,2}a_2 - \frac{dU}{dt}$$
$$\frac{da_2}{dt} = k_{t,1}a_1 - k_{t,2}a_2$$
$$\frac{dU}{dt} = k_r \cdot dilv_1 + k_b$$

If the classical two-volume model fails to identify, or estimate the distribution volume of the peripheral space V_2, the differential equations will collapse due to the division by V_2. By setting $k_{t,2} \cdot a_2 = k_{t,1} \cdot a^*$ we get the system:

$$\frac{da_1}{dt} = k_i(t) - k_{t,1} \cdot \left(a_1 - a^*\right) - \frac{dU}{dt}$$
$$\frac{da_2}{dt} = k_{t,1} \cdot \left(a_1 - a^*\right)$$
$$\frac{dU}{dt} = k_r \cdot dilv_1 + k_b$$

If we violate previous assumptions from volume kinetics, of the scaling between V_1 and V_2, letting $a^* = a_2$, a new bi-exponential model would take form. This model will converge for

both one and two-volume models [93] but with the loss of information about the scales between a_1 and a_2 and the translation of $k_{t,1}$ into k_t. Still, this model has the advantage of not dividing the fluid kinetic models into one- and two volume models. This model was used in paper II.

The concepts of fluid kinetics may be extended further to also take into account osmotic shifts, as in paper IV.

8 THESIS SUMMARY

$$\sum$$

8.1 PAPER I

Isoflurane Inhibits Compensatory Intravascular Volume Expansion After Hemorrhage in Sheep

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Peter Rodhe*
Christer H. Svensén, MD, PhD‡
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After hemorrhage, blood volume is partially restored by transcapillary refill, a process of spontaneous compensatory intravascular volume expansion that we hypothesized would be inhibited by anesthesia. Six chronically instrumented sheep were subjected to four randomly ordered experiments while conscious or during anesthesia with isoflurane. After plasma volume measurement (indocyanine green), 15% or 45% of the blood volume was withdrawn. To quantify transcapillary refill, mass balance and kinetic calculations utilized repeated measurements of hemoglobin concentration, assuming that transcapillary refill would dilute hemoglobin concentration. After 15% hemorrhage, mean arterial blood pressure remained stable in both conscious and isoflurane-anesthetized sheep (normotensive hemorrhage) but decreased after 45% hemorrhage (hypotensive hemorrhage). After either normotensive or hypotensive hemorrhage, transcapillary refill occurred more rapidly during the first 40 min than during the next 140 min ($P < 0.001$). In conscious sheep, at 180 min, 57% and 42% of the bled volume had been restored after normotensive and hypotensive hemorrhage, respectively, in contrast to only 13% and 27% ($P < 0.001$) in isoflurane-anesthetized sheep. A novel kinetic model implicated hemodynamic factors in rapid, early transcapillary refill and decreased plasma oncotic pressure in subsequent slower filling. We conclude that isoflurane inhibits transcapillary refill after both normotensive and hypotensive hemorrhage in sheep.

(Anesth Analg 2006;103:350–8)

After hemorrhage, blood volume is restored by a spontaneous process of compensatory intravascular volume expansion called "transcapillary refill," in which interstitial fluid enters the intravascular space and causes hemodilution (1). In humans, the refilling process requires 36 to 48 h and is inversely proportional to a gradual decline in hemoglobin concentration ([Hb]) (2). In experimental animals, a monoexponential wash-in function describes the course of compensatory intravascular volume expansion (3–5). Proposed mechanisms of transcapillary refill include an early decrease in capillary hydrostatic pressure (1,3) and a later increase in the total intravascular protein (4,5). Increased extracellular osmolality also translocates intracellular fluid to the extracellular fluid space (4). Transcapillary refill is markedly retarded if visceral perfusion is prevented (6) or if animals are dehydrated (7) or fasting (8), suggesting the involvement of the absorptive function of the intestinal mucosa (8). Increased intravascular protein might result from increased lymphatic flow or decreased transcapillary escape of protein as the oncotic gradient decreases (9). Mathematical models of transcapillary refill suggest that the refill rate is a function of hemorrhaged intravascular volume (10), arterial blood pressure (11), or an intracellular fluid shift (12). However, the influences of anesthetic drugs on transcapillary refill are unknown.

In the present study, we tested the hypothesis that isoflurane inhibits transcapillary refill in sheep subjected to 15% and 45% hemorrhage. After measuring baseline plasma volume, we calculated the rate of transcapillary refill from measurements of [Hb] and urinary excretion every 5 min for 180 min. We developed a kinetic model to examine the balance between hydrostatic and oncotic forces during intravascular volume restoration.

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METHODS

The protocol was approved by the institutional Animal Care and Use Committee and conformed to guidelines for the care of laboratory animals. At least 5 days before the planned experiments, 6 adult female merino sheep weighing 41 kg (median; range, 30–43 kg) were anesthetized with halothane in oxygen. A

Background

After hemorrhage, blood volume is partially restored by transcapillary refill, a process of spontaneous compensatory intravascular volume expansion [48, 84] that we hypothesized would be inhibited by anesthesia.

Methods

Six chronically instrumented sheep were subjected to four randomly ordered experiments while conscious or during anesthesia with isoflurane. After plasma volume measurement (indocyanine green), 15% or 45% of the blood volume was withdrawn. To quantify transcapillary refill, mass balance and kinetic calculations utilized repeated measurements of

haemoglobin concentration, assuming that transcapillary refill would dilute haemoglobin concentration.

Ethical considerations

The protocol was approved by the institutional Animal Care and Use Committee (IACUC) and conformed to guidelines for the care of laboratory animals.

Modelling

A system of ordinary differential equations, based on the Starling mechanism, was derived quantifying the contributions of hydrostatic and oncotic forces to the capillary refill on a whole-body level:

$$\frac{dV_p}{dt} = k_t\left(\frac{A_p}{V_p} - \frac{A_i}{V_i}\right) + k_p\left(V_p - V_{p,0}\right)$$

$$\frac{dA_p}{dt} = -k_a\left(\frac{A_p}{V_p} - \frac{A_i}{V_i}\right)$$

$$\frac{dA_i}{dt} = k_a\left(\frac{A_p}{V_p} - \frac{A_i}{V_i}\right) - R_a\left(\frac{A_p}{V_p} - C_{p,0}\right)$$

where V_p and V_i is plasma and interstitial fluid volumes, respectively, A_p and A_i is the amount of colloidal protein in the plasma and interstitial fluid volumes, t is time (min), k_t is an oncotic flow coefficient (ml^2 g^{-1} min^{-1}), k_p is a pressure-compliance coefficient (min^{-1}), k_a is a colloidal flow coefficient (ml min^{-1}) and R_a is a colloidal turn-over rate coefficient (ml min^{-1}).

The four unknown parameters in the model (k_t, k_p, k_a, and R_a) were estimated for each experiment separately using Matlab 6.51 (MathWorks, Natick, MA). Input parameters were the measured plasma volume (V_p) at baseline, initial values for the amount of protein in the plasma

(A_p) and interstitial fluid volumes (A_i), in which the baseline interstitial fluid volume was approximated to be 15% of the body weight. The protein concentration at 180 min was used as $C_{p,0}$. The solution of the differential equations was then fitted to the plasma volume as indicated by the data on Hb dilution.

Results

All animals tolerated all 4 experiments well, except for one conscious sheep in which hypotensive hemorrhage was terminated because of a clotted pulmonary arterial catheter.

After 15% hemorrhage, mean arterial blood pressure remained stable in both conscious and isoflurane-anesthetized sheep (normotensive hemorrhage) but decreased after 45% hemorrhage (hypotensive hemorrhage). After either normotensive or hypotensive hemorrhage, transcapillary refill occurred more rapidly during the first 40 min than during the next 140 min ($p < 0.001$). In conscious sheep, at 180 min, 57% and 42% of the bled volume had been restored after normotensive and hypotensive hemorrhage, respectively, in contrast to only 13% and 27% ($p < 0.001$) in isoflurane-anesthetized sheep.

In 21 of 23 experiments, we could quantify the influences of hydrostatic and oncotic forces on transcapillary refill by kinetic analysis. In the remaining 2 experiments, data were too scattered to allow estimation of all 4 parameters. The result suggests that transcapillary refill reduced the intravascular colloid osmotic pressure by diluting the plasma protein concentration, which slowed further transcapillary refill. Using parameters derived from kinetic analysis, simulations illustrate that both the hydrostatic and colloid osmotic forces are weaker in the presence of isoflurane than in the awake state.

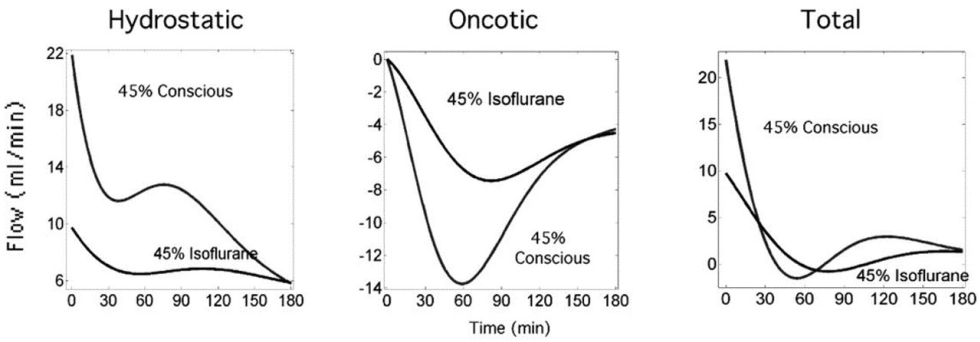

Figure 20. The transcapillary flows, as separated by the mathematical model.

Conclusions

We concluded that isoflurane inhibits transcapillary refill after both normotensive and hypotensive hemorrhage in sheep.

8.2 PAPER II

Arteriovenous Differences in Plasma Dilution and the Distribution Kinetics of Lactated Ringer's Solution

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Joel Olsson, MD, PhD*
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BACKGROUND: Conventional concept suggests that infused crystalloid fluid is first distributed in the plasma volume and then, since the capillary permeability for fluid is very high, almost instantly equilibrates with the extracellular fluid space. We challenge whether this view is consistent with findings based on volume kinetic analysis.
METHODS: Fifteen volunteers received an IV infusion of 15 mL/kg of lactated Ringer's solution during 10 min. Simultaneous arterial and venous blood hemoglobin (Hgb) samples were obtained and Hgb concentrations measured. The arteriovenous (AV) difference in Hgb dilution in the forearm was determined and a volume kinetic model was fitted to the series of Hgb concentrations in arterial and venous blood.
RESULTS: The AV difference in plasma dilution was only positive during the infusion and for 2.5 min thereafter, which represents the period of net flow of fluid from plasma to tissue. Kinetic analysis showed that volume expansion of the peripheral fluid space began to decrease 14 min (arterial blood) and 20 min (venous blood) after the infusion ended. Distribution of lactated Ringer's solution apparently occurs much faster in the forearm than in the body as a whole. Therefore, the AV difference in the arm does not accurately reflect the distribution of Ringer's solutions or whole-body changes in plasma volume.
CONCLUSIONS: The relatively slow whole-body distribution of lactated Ringer's solution, which boosts the plasma volume expansion during and for up to 30 min after an infusion, is probably governed by a joint effect of capillary permeability and differences in tissue perfusion between body regions.
(Anesth Analg 2009;108:128–33)

Crystalloid fluids, such as lactated Ringer's solution, are commonly used during anesthesia and surgery. When infused into the circulation hemodilution occurs which correlates with the increase in plasma volume (PV). Therefore, hemoglobin (Hgb) changes have been used to indicate the PV or blood volume (BV) over time,[1–6] although the large-vessel: whole-body hematocrit (Hct) ratio of 0.9 should be applied to correct for anticipated unequal distribution of the Hgb molecules.[6–7] Since fluid can be assumed to distribute faster than molecules of any size, infused fluid is believed to simultaneously and almost instantly spread throughout the PV and extracellular fluid space.

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This conventional "physiological view" is rational[6,8] but has been challenged by volume kinetics in which crystalloid fluid becomes distributed between two functional body fluid spaces over a period of time, as long as 20–30 min.[10–13] The relatively slow distribution process is of clinical relevance since it implies that the IV expansion during and shortly after administration is much greater than the 20%–25% of the infused volume suggested by the physiological view model. Moreover, the reason for slow distribution is unclear. The time might be too long to be explained solely by local equilibration of fluid across the capillary membrane, and we have questioned whether Hgb changes also reflect differences in tissue perfusion.[14]

This issue can be explored by comparing the Hgb level in arterial and venous samples (arteriovenous [AV] difference) simultaneously by a kinetic analysis. The AV difference shows the direction of the fluid flux between plasma and the interstitial fluid space in the vicinity of the venous sampling site (Fig. 1), whereas volume kinetics can be used to indicate the direction of the fluid flux for the whole body (Fig. 2). Hence, the purpose of this study in volunteers was to compare the direction of fluid flow based on AV differences and the direction of fluid flow as obtained by volume kinetic analysis. Moreover, we wanted to examine the similarity of the kinetic parameters when based on

Background

Crystalloid fluids, such as lactated Ringer's solution, are commonly used during anesthesia and surgery. When infused into the circulation, hemodilution occurs which correlates with the increase in plasma volume. Therefore, haemoglobin (Hb) changes have been used to indicate the plasma or blood volume over time [85-87] although the large-vessel: whole body hematocrit (Hct) ratio of 0.9 should be applied to correct for anticipated unequal distribution of the Hb molecules [87-90].

Since fluid can be assumed to distribute faster than molecules of any size, infused fluid is allocated to parts of the plasma volume and adjacent areas of the peripheral space that are easily perfused [91].

The conventional view suggests that infused crystalloid fluid is first distributed in the plasma volume and then, since the capillary permeability for fluid is very high, almost instantly equilibrates with the extracellular fluid space [92].

Methods

Fifteen volunteers received an IV infusion of 15 ml/kg of lactated Ringer's solution during 10 min. Simultaneous arterial and venous blood haemoglobin (Hb) samples were obtained and Hb concentrations measured.

The arteriovenous (AV) difference in Hb dilution in the forearm was determined and a volume kinetic model [93] was fitted to the series of Hb concentrations in arterial and venous blood to quantify this effect.

The kinetics of the IV infused fluid was modelled separately for each subject, using Matlab version 7.0.1 (Math Works, Notich, MA), whereby a nonlinear least-squares regression routine based on a modified Gauss-Newton method was repeated until none of the three unknown parameters (V_1, k_t, and k_r) changed by more than 0.001 (0.1%) in each iteration. No correction was applied for the transit time for blood between the radial artery and the cubital vein since we believed this would be <10 s.

Ethical considerations

The study was approved by the Institutional Animal Care and Use Committee, University of Texas Medical Branch at Galveston, Texas, USA.

One issue was the insertion of an arterial line. There is a slight possibility of complications. However, this was necessary because of the aim of comparing the arterial and venous Hb dilution (A-V difference).

Less than 200 ml of blood was drawn from each subject. A normal blood donor gives about 400 ml of blood.

Results

The AV difference in plasma dilution was only positive during the infusion and for 2.5 min thereafter, which represents the period of net flow of fluid from plasma to tissue. Kinetic analysis showed that volume expansion of the peripheral fluid space began to decrease 14 min (arterial blood) and 20 min (venous blood) after the infusion ended.

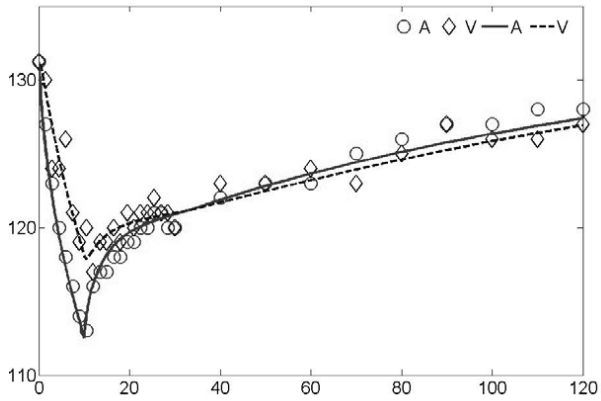

Figure 21. Example of an arterial-venous Hb data and model fit by a lumped parameter model of 10 compartments.

Conclusions

Distribution of lactated Ringer's solution apparently occurs much faster in the forearm than in the body as a whole. Therefore, the AV difference in the arm does not accurately reflect the distribution of Ringer's solutions or whole-body changes in plasma volume.

The relatively slow whole-body distribution of lactated Ringer's solution, which boosts the plasma volume expansion during and for up to 30 min after an infusion, is probably governed

by a joint effect of capillary permeability and differences in tissue perfusion between body regions.

Analysis and observations relevant of the thesis

In paper II, we refer to V_1 and V_2 as *functional spaces* and not *physiological*. But in the fluid kinetic section, we stated that $v_p = v_1$. The reason for this is because we assume that information of v_p is lost when only considering the dilution of V_p. However, the coupling between V_1 and V_p is clearly strong, because of the underlying assumption of Hb-dilution. Furthermore, we showed in this paper, for arterial samples, we got an almost 1:1 correlation between the Nadler-formula of V_p, and the computed central space V_1, from arterial Hb-data.

For a closed expandable compartment, with Hb as a dilution tracer, we found out that the plasma volume was given by:

$$V_p = V_i \cdot \frac{\left(1 - HCT(0)\right)}{\left(\frac{C_{Hb}(0)}{C_{Hb}(T)} - 1\right)}$$

If we apply this relationship onto the subjects, where the infusion time was 10 minutes, and the rate of infusion was 1.5 ml/min/kg of lactated Ringer´s solution, we may compute an estimation of the plasma volume. If we chose to correct the *Hct* by 0.9 and compute three values of V_p at t = 3, 6, 9. Then we may estimate the mean

$$\tilde{V}_p = \frac{\left(3 \cdot V_p(3) + 2 \cdot V_p(6) + 1 \cdot V_p(9)\right)}{3 + 2 + 1},$$

and for this estimation we choose to put weights. Firstly, I make use of the arterial data. When comparing these results by the plasma volume predicted by Nadler et al., we find a convincing agreement (k = 1.05, p< 0.05, N=13). See Figure 22.

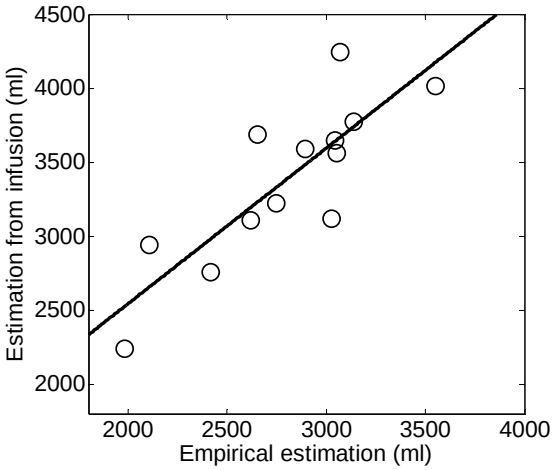

Figure 22. (Arterial data) Comparison of estimation of V_p from an crystalloid infusion (y-axis) and an empirical formula developed by Nadler et al. (x-axis).

Now, if we redo the computation on the venous side, we will see that our model looses agreement with the Nadler formula. See Figure 23.

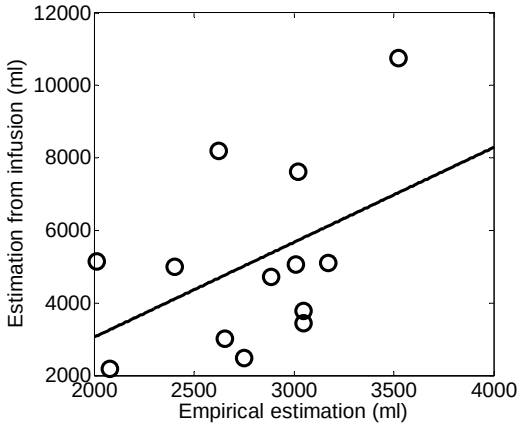

Figure 23. (Venous data) Comparison of estimation of V_p from an crystalloid infusion (y-axis) and an empirical formula developed by Nadler et al. (x-axis).

If we compare Figure 22 and Figure 23, we can see a more pronounced variability of the venous sampling.

From this we may conclude that arterial Hb seems to reflect the plasma volume expansion even if considered as a closed volume, and at least initially during infusion. Furthermore, in this paper, we concluded that the sampling curves showed similar profiles. Despite the similarities, the venous data overestimates the plasma volume grossly according to figure 8. When applying a fluid kinetic model as in paper II, these estimations were thus improved significantly (*arterial*: $k = 1.00$, $r = 0.7$, $p < 0.001$; *venous*: $k = 1.37$, $r = 0.69$, $p < 0.01$).

However, this relationship is not usually explored, since sampling is hampered by the requirement of an arterial line which is considered to be an invasive operation that can cause damage to the vessel. When sampling venous data, we analyze only locally mixed blood that previously went through a filtration process through the capillary bed. Interstitial fluid spaces in the lungs probably become expanded quickly and easily, whereas some of the lactated Ringer's solution might not even reach the interstitium of poorly perfused areas with resting muscle. The Hb changes of the arterial blood represent the sum of all such occurrences, while the venous blood reflects the arterial blood including the local tissue effects.

Therefore, further experiments has to be carried out, in order to find out during what circumstances this holds for and how the clinicians may compute the blood volume using only Hb as a tracer.

The fluid homeostasis mainly (or ideally) depends on the daily intake of salt and water. During hypervolemia, due to release of ANP and the increased filtration pressure, urine output will increase significantly (see Figure 8). On the other hand, during hypovolemia, the basal diuresis will decline and eventually, during hypovolemic shock, it may be blunted.

During fluid therapy, or as a result of a wide range of different pathological states, the fluid homeostasis will shift its baseline (steady state). That leads us to the question: would it be possible to analyze fluid distribution using math models when baselines are shifting due to

differences in hydration levels? Can this be done by giving our patients small quick boluses to find out their responses?

Considering this trial where the subjects were not allowed to drink or eat the day before the experiments, obviously, they were to some degree dehydrated before they received iv fluids.

By examining the results, the fluid infusion seemed to change their previous steady state. As we can see in Figure 24, the infusion even caused three of the subjects to drop their plasma volumes.

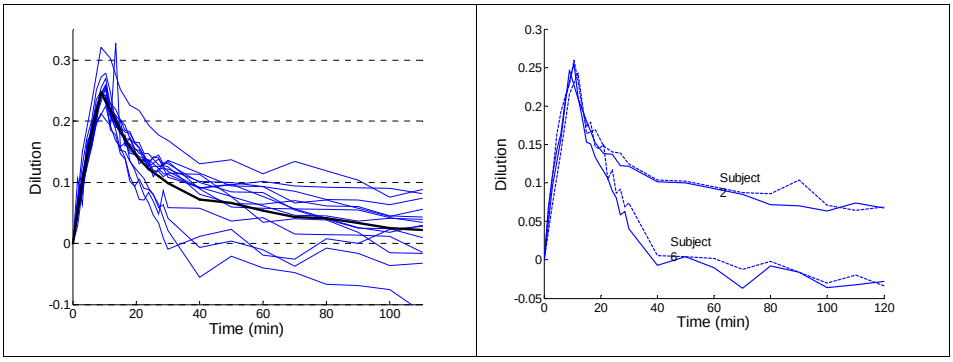

Figure 24. Left: Spaghetti-plot of dilution (thin lines) and mean (thick line) (arterial data). Right: Two subjects chosen. Solid line represents arterial dilution and dashed line venous dilution.

As an example of the modelling process, we will go through the process step by step.

1. Fluid kinetic model

First, we consider the fluid kinetic model:

$$\frac{dv_1}{dt} = k_i(t) - k_p \cdot (a_1 - \mu \cdot a_2) - \frac{dU}{dt}$$
$$\frac{dv_2}{dt} = k_p \cdot (a_1 - \mu \cdot a_2) \quad ,$$
$$\frac{dU}{dt} = k_r \cdot a_1 + k_b$$

where $k_r = 0$ if $a_1 < 0$. In this system of ODE, we transformed the dilution and the parameter k_t (see section Fluid kinetics) by

$$k_p = \frac{k_t}{V_1}, \mu = \frac{V_1}{V_2},$$

subsequently, the model has 5 parameters to be considered: k_p (min^{-1}), V_1 (ml), k_r (min^{-1}), μ, k_b (ml/min).

2. Discrimination of models

For this example, we choose to investigate the residual sum of squares, *RSS*, and perform a F-test as an estimation of discrimination between rival models [94]. Six rivaling models were chosen

Model	k_p	V_1	k_r	μ	k_b
1	X	X	X	X	X
2	X	X	X	X	0
3	X	X	X	1	X
4	X	X	X	1	0
5	0	X	X	0	X
6	0	X	X	0	0

Table 3. Discrimination test of six models where X is to be estimated

Choosing subject 2, venous data, (see figure 25, right plot), we get the result:

Model	k_p	±σ	V_1	±σ	k_r	±σ	μ	±σ	k_b	±σ
1	0.059	0.004	3575	753	0.0000	0.0078	0.52	0.12	2.6	2.5
2	0.040	0.007	3984	898	0.0073	0.0003	0.69	0.02	0	0
3	0.050	0.010	3775	852	0.0102	0.0026	1	1	0.8	2.0
4	0.048	0.011	3794	863	0.0121	0.0023	1	1	0	0
5	0	0	4537	1010	0.0555	0.0122	0	0	-19.8	5.1
6	0	0	5103	1055	0.0153	0.0031	0	0	0	0

Table 4. Parameter estimation of six models. σ is the estimated standard deviation of each parameter.

Next step was to compute the residuals and perform the F-test:

Test (T-N)	RSS_T	RSS_N	*F-test*
1-2	0.002878	0.00273	0
1-3	0.002878	0.002609	0
1-4	0.002878	0.002589	0
1-5	0.002878	0.003312	0
1-6	0.002878	0.010937	1
2-4	0.00273	0.002589	0
2-6	0.00273	0.010937	1
3-4	0.002609	0.002589	0
3-5	0.002609	0.003312	0
3-6	0.002609	0.010937	1
4-6	0.002589	0.010937	1
5-6	0.003312	0.010937	1

Table 5. Residual sum of squares and the F-test. RSS_N is residual sum of squares of the nested model N, which is tested against the model T with RSS_T. p = 0.05 was chosen as significance level in the F-test.

The F-test suggests that model 6 were discriminated by all models. Moreover, test 1-N, 2-N and 3-N suggested that we did not get any significantly better fit by the T model. What are left are models 4 and 5. Looking closer at the estimates, and comparing the RSS, model 5 gives an ambiguos estimate of k_b, probably due to compensation of peripheral upload since it lacks the k_t parameter. Hence, we conclude that for subject 2, model 4 would be the model to choose and it is likely that we may set $\mu = 1$ and $k_b = 0$.

3. Extending the model

As discussed earlier, it is clear that some of the subjects change their baseline during infusion, and it would be of clinical relevance of estimating this shift. Therefore, we added the parameter a_{ref} which allowed the model to adapt a new-steady state central volume. Normally, we would model this baseline shift by a sigmoid function. However, such approach would increase the number of parameters by two. Therefore we instead assumed that a_{ref} is the daily homeostatic baseline – the shift of baseline occurred during night before the experiment. Then a_{ref} is constant from $t = 0$.

Subject	$a_{ref,artery}$	$\pm\sigma$	$a_{ref,vein}$	$\pm\sigma$	*F-test A*	*F-test V*
1	-128	83	-84	171	0	0
2	-228	89	-133	117	1	0
3	8	10	27	39	0	0
4	-80	45	65	79	1	0
5	49	6	131	25	0	0
6	-75	28	-83	36	1	1
7	79	4	163	12	1	0
8	-16	14	-53	38	0	0
9	-730	530	-829	1119	1	1
10	-45	15	-39	28	1	0
11	-6	32	2	30	0	0
12	63	9	44	64	1	0
13	-461	143	190	27	1	0
14	-76	47	-54	68	1	0
15	97	17	-293	714	1	0

Table 6.

From Table 6, we show the result of the two models, the nested with $a_{ref} = 0$ and the full where a_{ref} was estimated. This was done both for arterial and venous samples. The F-test on arterial side suggested that for 5 of the subjects, it was more likely that $a_{ref,artery}$ was zero. But for ten of the subjects, the F-test, with $p = 0.05$, showed a significance when adding $a_{ref,artery}$

to the model. However a_{ref} in general, seems to be more or less negligible -44 (-115 – 4)[24] when considering the small amount in millilitres the baseline actually was shifted, and with concerns about the general high standard deviation of the estimates. But what was of clinical relevance, was that three of the subjects seemed to be dehydrated before the infusion (-228, -730, -461).

On the venous side, only two of the subjects gained a significant improvement of using a_{ref} according to the F-test. Despite this weak indication of homeostatic baseline, we chose to present a_{ref} in paper II, for future work of finding a patient basal volume.

[24] Median and range. These results differs slightly from those reported in paper II: -43 (-85 – 2), due to different optimization methods.

8.3 PAPER III

Modelling of peripheral fluid accumulation after a crystalloid bolus in female volunteers - a mathematical study

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Background

There is an overwhelming consensus that excessive peripheral fluid accumulation, causing weight-gain postoperatively is detrimental [69]. Therefore, the clinician should benefit from being able to continuously monitor such fluid accumulation that sometimes occurs during per-operative fluid therapy. In order to better understand the dynamics of hypervolemia and the renal response to excess fluid, we aimed at modelling plasma dilution and urinary output simultaneously in volunteers.

Methods

Ten healthy female non-pregnant volunteers, aged 21-39 year (mean 29), with a bodyweight of 58-67 kg (mean 62.5 kg) participated. No oral fluid or food was allowed between midnight and completion of the experiment. The protocol included an infusion of acetated Ringer's solution, 25 ml/kg over 30 minutes. Blood samples (4 ml) were taken every five minutes during the first 120 min, and thereafter the sampling rate was every 10 Min until the end of the experiment at 240 min. A standard bladder catheter connected to a drip counter to monitor urine excretion continuously was used. The data were analyzed by empirical calculations as well as a mathematical model.

The kinetic model had eight unknown parameters: k_t, k_{el}, k_b, σ, μ, T_u, T_1, T_e.

$$\frac{da_1}{dt} = k_I \cdot \sigma - \frac{k_t}{v_{1,0}} \cdot (a_1 - \mu \cdot a_2) - e(t)$$
$$\frac{da_2}{dt} = k_I \cdot (1-\sigma) + \frac{k_t}{v_{1,0}} \cdot (a_1 - \mu \cdot a_2)$$
$$\frac{da_E}{dt} = e(t) - u(t)$$

where

$$e(t) = k_b \cdot e^{\frac{k_{el} \cdot a_1^*}{v_{1,0}}} \qquad a_1^* = a_1(t - T_1)$$
$$u(t) = \frac{a_e}{T_e}$$
$$u_{output} = u(t - T_u)$$

Estimates of the unknown parameters in the fluid space models were obtained by using the MatLab function *fminsearch*, which uses a simplex search method [95]. The differential equations were solved by the MatLab function *dde23* suitable for delay differential equations [96].The minimizing function computed the equally weighed residuals of plasma volume expansion (a_1) and urine output (u_{output}).

Ethical considerations

The study was approved by Ethical Review Board of the Stockholm County.

The total amount of blood drawn was less than 200 ml. One ethical concern was the insertion of a urinary catheter. There is an increased risk of infection in the urinary tract. Also, some mechanical damage to the urinary tract can be caused. Since this paper was to investigate the coupling between plasma volume expansion and urinary output, this device was crucial for the experiment.

Results

Maximum urinary output rate was found to be 19 (13 – 31) ml/min. The subjects were likely to accumulate three times as much of the infused fluid peripherally as centrally; $1/\mu = 2.7$ (2.0 – 5.7). Elimination efficacy, E_{eff}, was 24 (5 – 35) and the basal elimination k_b was 1.11 (0.28 – 2.90). The total time delay T_{tot} of urinary output was estimated to 17 (11 - 31) min.

Conclusions

The experimental results showed a large variability in spite of a homogenous volunteer group. It was possible to compute the infusion amount, plasma dilution and simultaneous urinary output for each consecutive time-point and thereby the empirical peripheral fluid accumulation. The variability between individuals may be explained by differences in tissue and hormonal responses to fluid boluses which need to be further explored.

Analysis and observations relevant to this thesis

Elimination is modelled by [97-98]:

$$\frac{dU}{dt} = k_r \cdot dilv_1 + k_b$$

Where we require that $k_r = 0$ if $v_1 < 0$. In Figure 25, two subjects from this paper were chosen to illustrate the linearity. Subject 3, on the left figure, seem to fit the elimination model. However, subject 4, on the right figure, shows a more scattered appearance.

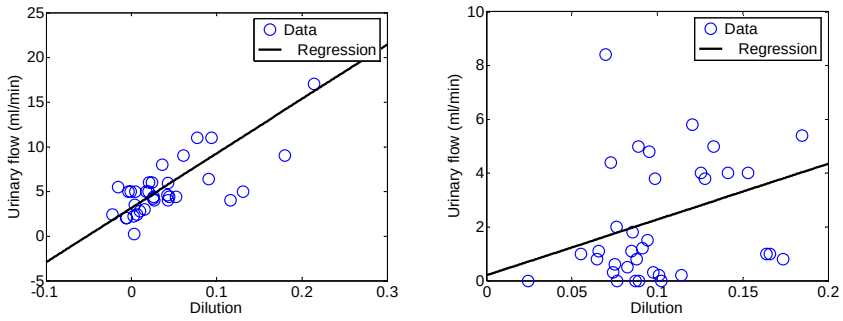

Figure 25. Left figure (subject 3): k_r = 61.0 ml/min, k_b = 3.2 ml/min, r = 0.67, p < 0.01. Right figure (subject 4): k_r = 20.8 ml/min, k_b = 0.2 ml/min, r = 0.09, p > 0.05.

If we make an approach, that the renal output is more likely to be governed by an exponential model with a delay, the model would take the form

$$\frac{dU}{dt} = k_b \cdot e^{-k_{el} \cdot dilv_1 (t - T_1)}.$$

If we redo the computation of subject 4, in paper III by this model, setting the delay to T_1 = 15 min, we get the results, as plotted in Figure 26.

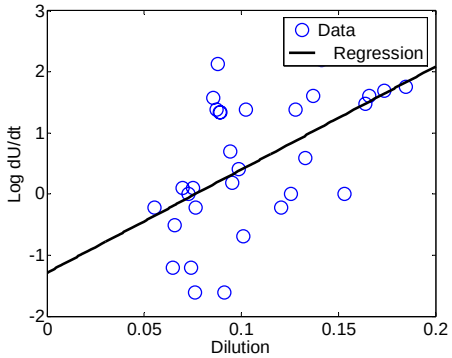

Figure 26. Subject 4 (exponential model): k_{el} = 16.9, k_b = 0.28 ml/min, r = 0.30, p < 0.01.

From figure 14, we may conclude that subject 4 was more likely to follow the exponential delay elimination model. It is even more likely that the elimination as a function of plasma volume expansion should have a sigmoid appearance, as in Figure 27.

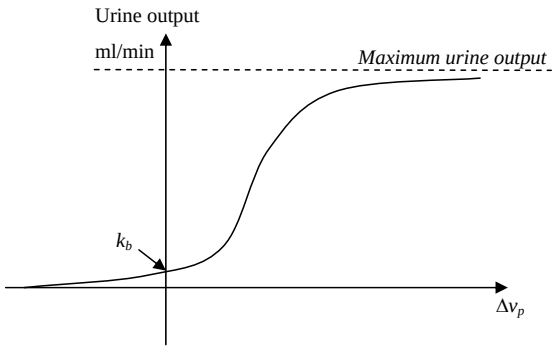

Figure 27. Theoretical relationship between urine output and plasma volume expansion.

During the modelling phase in this work, this relationship was examined by approximating the hypothetical urine output curve by this sigmoid function

$$\frac{dU}{du} = \frac{A}{2}\left(\tanh\left(c \cdot \left(dilv_p(t - T_c) - \beta\right)\right)\right).$$

An example of a test run is shown in Figure 28.

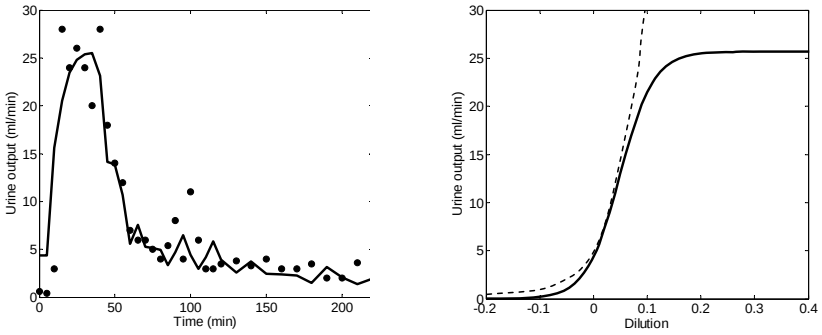

Figure 28. Fitting of urine output. The right figure shows the sigmoid fitted function. The dashed line illustrates an exponential equivalent model.

From figure 26, we may conclude that our hypothesis agrees with data for this specific subject. However, the experiment was not from the beginning designed to fully examine this relationship why several of the subjects failed to identify all parameters needed. To examine the full range of this sigmoid curve, it was necessary to make the subjects both hypovolemic and give them drastically different infusion rates. This is by natural ethically questionable to do with volunteers and has to be performed in an animal model, preferably. Thus, the exponential equation worked well for this particular range of the sigmoid curve.

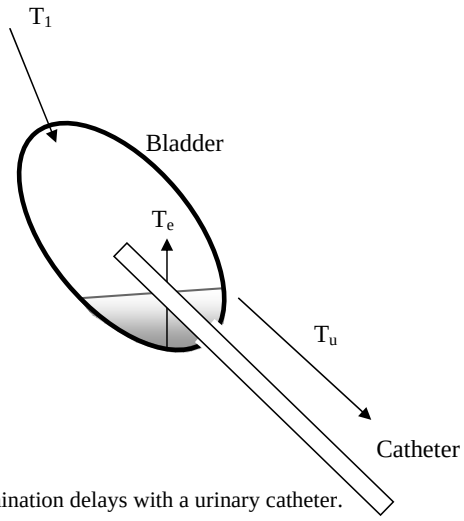

Figure 29. Elimination delays with a urinary catheter.

Three different time delays were needed to fit all subjects in the same model. T_1 reflects the delay of the renal response to hypervolemia. T_e is probably due to a filling time within the bladder, before it reaches the top of catheter. Finally, T_u is the pathway from the tube, to the actual measurement, see Figure 29.

As concluded in the discussion in Paper II, the complex and fairly long distribution process of crystalloids explains indirectly why we cannot be sure that V_1 equals the baseline plasma volume. Furthermore, we concluded from the results that if we infuse a bolus of lactated Ringer's solution into the plasma, some of the fluid will have left this physiological space even before the rest of it has become distributed throughout the entire plasma volume. This problem was dealt with in this paper, by inferring a bypass flow ratio σ that reflects a fast equilibration of fluid into the more easily perfused parts of the interstitium. In presence of such a fluid route, during infusion, the central fluid space might be overestimated.

In summary, we concluded that in presence of simultaneously monitoring and computation of the size of central fluid space and urine output, the clinician would get an improved estimation of this peripheral accumulation and thereby be able to individualise the fluid therapy.

8.4 PAPER IV

A comparison of fluid distribution in old and young volunteers given 2.5% glucose solution orally and intravenously

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Background

The aim of this study was to compare two fluid administration routes, oral and intravenous administration in a young and an elderly group of healthy volunteers. We wanted to investigate differences in absorption of fluid, fluid distribution and its elimination in an elderly versus a young population.

Our hypotheses were that there should be a lag time between orally and intravenously given fluids as regards to absorption. Older subjects will have a slower elimination of fluid and plasma glucose. Furthermore, orally given fluids will have a more prolonged volume effect.

Methods

Twenty four volunteers were recruited by responding to advertisements and gave their written consent to participate in the study. The subjects were enrolled in age groups, a young group (age 18-25) and an elderly group (age 70-90). Exclusion criteria were pregnancy, dementia, diabetes, medication with diuretics, cardiac failure classified according to New York Heart Association (NYHA) III-IV and/or angiotensin converting enzyme inhibitors (ACEI).

On separate occasions, the subjects in both groups were given a crystalloid 25 mg/ml glucose solution, either orally (ORAL) or intravenously (IV) in a crossover design with at least two weeks in between.

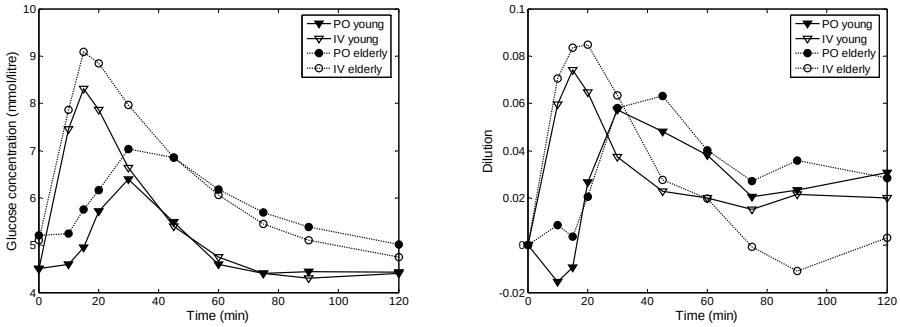
On each occasion, the subjects got 7 ml/kg of the crystalloid solution during 15 minutes. During the ORAL experiment the fluid was administered in fifteen cups, where each cup represented 1/15 of the total amount. In the IV group, the administration of fluid was administered by the aid of an infusion pump.

Ethical considerations

The study was approved by the Ethical Review Board in the Stockholm County. All patients were subject of intravenous cannulation, which may cause discomfort during perforation. 70 ml of blood was drawn at total, which is considered to be a small amount.

Results

All subjects went through the experiments and there were no complications. The mean curves of glucose concentration and dilution of plasma volumes were plotted in Figure 30.



A. Glucose concentration profile **B. Plasma dilution profile**

Figure 30. Shows the pooled data of glucose concentration and plasma dilution for the four groups. In Fig A, the group of elderly eliminates glucose slower than the younger group. In Fig B, the plasma dilution effect of the young group, given fluid orally, shows a reduction intially. Furthermore, the elimination of the plasma volume is more pronounced when fluid is given intravenously.

The bioavailability crystalloid glucose solution was estimated to:

$F_{elderly}$ = 0.65 (0.60 - 0.69)
F_{young} = 0.70 (0.59 -0.94)

And the bioavailability of the volume effect was estimated to be:

$F_{elderly}$ = 1.06 ± 0.51
F_{young} = 0.93 ± 0.59

Data are presented as median and ranges. Also, the lag-time of glucose given orally was estimated to be 17 (8 – 25) min for the younger group and 18 (13 – 22) min for the elderly. For fluid, the lag-time was estimated to 29 (21 - 34) min for the younger and 25 (16 – 39) min for the elderly.

Furthermore, we computed the half-life of raised glucose levels:

	$t_{1/2}$ (min)
PO-young	3.8 (3.1 - 11.9)
IV-young	16.1 (14.8 - 23.0)
PO-elderly	30.5 (22.3 - 55.9)
IV-elderly	41.6 (23.8 - 54.6)

And finally, we computed the elimination efficacy of fluid:

	E_{eff} (ml/min)
PO-young	66.2 (13.6 - 106.3)
IV-young	15.3 (6.4 - 49.2)
PO-elderly	25.0 (8.0 - 44.5)
IV-elderly	17.6 (8.0 - 46.6)

Conclusions

The data showed larger variations for the fluid kinetic calculations than for the glucose kinetics. As expected there was a significant lag time between orally and intravenously administered fluid, both for glucose and volume effect. Elderly subjects tended to eliminate glucose slower than younger as expected. Surprisingly, the younger subjects showed a more persistent tendency to keep the administered fluid than the elderly.

Analysis and observations relevant to this thesis

The glucose model could likely be improved by adding data for insulin and C-peptide. In summary, it was possible to use mathematical application to model the distribution of both oral and intravenous administration of fluid to young and old volunteers. The kinetic computations quantified the renal efficacy, volume effects, lag times, half-life of glucose, glucose clearance and base-line shifts of glucose. The bioavailability test of various fluids, stratifying for gender or age for example, may become a useful tool for future investigations in fluid therapy.

9 DISCUSSION AND CONCLUSION

The aim of this thesis was to find mathematical applications to clinical problems. The clinicians work may be regarded as an open loop system, responding to a finite set of clinical parameters. These clinical assumptions may be modelled in some way, and eventually evaluated towards clinical signs and patient outcome. If the mathematical model, end-points and clinical observations give an adequate outcome for the patient, then we may conclude that theory and practice comes together. Furthermore, we may use the mathematical models to check that therapy aim towards clinical goals.

Extending this conclusion further, we may in the future develop closed loop systems, where fluid is administered solely by an autopilot – in the same manner as ventilators or target control infusion for drugs (TCI).

This thesis has shown that it is possible to use mathematical models to solve pertinent clinical problems, or at least quantify clinically useful parameters from the full-body effects induced by fluid therapy or bleeding.

Though, there are several weaknesses identified. One major problem is the lack of relevant data to enhance the models (ions, hormones, cardiac output, oncotic pressure etc). Another weakness is the surprisingly large variability of Hb-data. In the appendix, I show an example of an *ad hoc* method to compare Hb data between the studies II - IV. This computation gives us a hint in how the quality of Hb data may differ between the studies. Interestingly, the group of elderly showed a more scattered behaviour than the young group ($P < 0.05$, t-test, unpaired) though they belonged to the same study (IV). These biases are probably a combined effect of differences in vein constitution, the technique of the clinician and presumable differences in coagulation factors. Furthermore, the use of iterative sampling of haemoglobin invasively is not clinically feasible. The need of an accurate and reliable non-invasive monitor of Hb is therefore essential for the future.

Furthermore, we need to develop devices that continuously monitor urine output in a non-invasive fashion without interfering with surgical procedures. With these two devices, the clinician would know more precisely about the fluid shifts within the body, and be able to detect any peripheral upload.

Moreover, during the modelling processes in this thesis, a number of simulators were developed in order to validate or examine hypothesis, from microvascular to full-body simulators. One problem of building such simulators, are the great number of parameters that are needed to fully explain perturbations of fluid homeostasis during fluid infusion. If models get too complicated they will not benefit clinicians in daily practice.
Still: we do need realistic simulators for the future, for research and education. By the incremental growing knowledge in fluid therapy, mathematical modelling of full-body effects as well as isolated microvascular processes, through pre-clinical research, faster computers etc, full-body simulators will become more interesting tools.

My final conclusion is that mathematical modelling of clinical applications improves the understanding of fluid therapy. It is possible to continuously model fluid behaviour in the body as seen in Papers II-III particularly. This should enhance the understanding of accumulating oedema in the body which is an apparent problem for all clinicians. Current research in the last decade focus on rigid or goal directed protocols which may be closer to the truth than previous standard of care regimes. They can, however, never *exactly*, reveal the fluid distribution at every time point. This can be done by the help of mathematical models which should move this area of research substantially forward.

10 APPENDIX

Variability and quality of Hb data

Suppose we knew the error-free Hb distribution $\Omega_{Hb}(t)$. Then, we measure Hb values as $\Theta = \{\theta_1(t_1), \theta_2(t_2), \ldots \theta_N(t_N)\}$.

Firstly, we define the integral R_θ to quantify the absolute difference between observed Hb and the real Hb:

$$R_\theta = \int_{t_1}^{t_N} |\Omega_{Hb}(t) - f_\theta(t)| dt$$

where $f_\theta(t) = \theta_i + (\theta_{i+1} - \theta_i) \cdot \frac{t - t_i}{t_{i+1} - t_i}, t_i \le t \le t_{i+1}$

Then we define:

$$\rho_q = \frac{R_\theta}{\int_{t_1}^{t_N} |\Omega_{Hb}(t)| dt}$$

Thus, we normalize R_θ.

There are many choices of approximating $\Omega_{Hb}(t)$. One way is to compute the dilution from $\theta_1(t_1)$ to $\theta_1(t_N)$ and fit a kinetic model. However, a more general way, which can be applied directly onto the observed Hb, is by smoothing the data.

We may for example use *weighted moving average* WMA, with n = 5. Then, if we choose a typical monoexponential solution to a kinetic problem, and smooth the data J times.

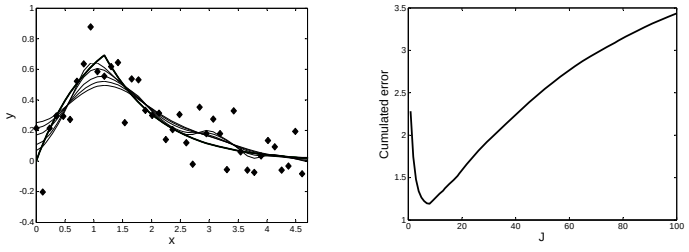


Figure 31. Left: An underlying exponential function (thick line), normal distributed errors (diamonds, STD=0.15) and smoothing curves for J = 5, 10, 20, 30, 40 (thin lines). Right: The cumulated error as a function of the number of smoothing runs by WMA.

From figure 16, for this specific run, J = 8 gave the best fit of the underlying distribution. Approximating $\Omega_{Hb}(t)$ by $\Delta_J\Theta$, where Δ_J is the smoothing operator, applied J times, and moreover, if we approximate the integrals by *trapezoidal method*, we finally get:

$$\rho_q^J = \frac{trapz\left(\left|\Delta_J\Theta - \Theta\right|\right)}{trapz\left(\left|\Delta_J\Theta\right|\right)}$$

Without formalizing this mathematics any further, we will give numerical examples of the studies conducted in the thesis, using J = 3, n = 5 and computing mean and standard deviation, we get the result:

4.5 ± 0.5 (artery data, work II)

6.2 ± 2.7 (vein data, work II)

6.7 ± 1.4 (vein data, work III)

7.6 ± 2.9 (vein data, work IV, young)

9.4 ± 3.1 (vein data, work IV, old)

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