Diplomarbeit

Body Composition in Haemodialysis Patients

eingereicht von

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Graz, am 08.07.2010

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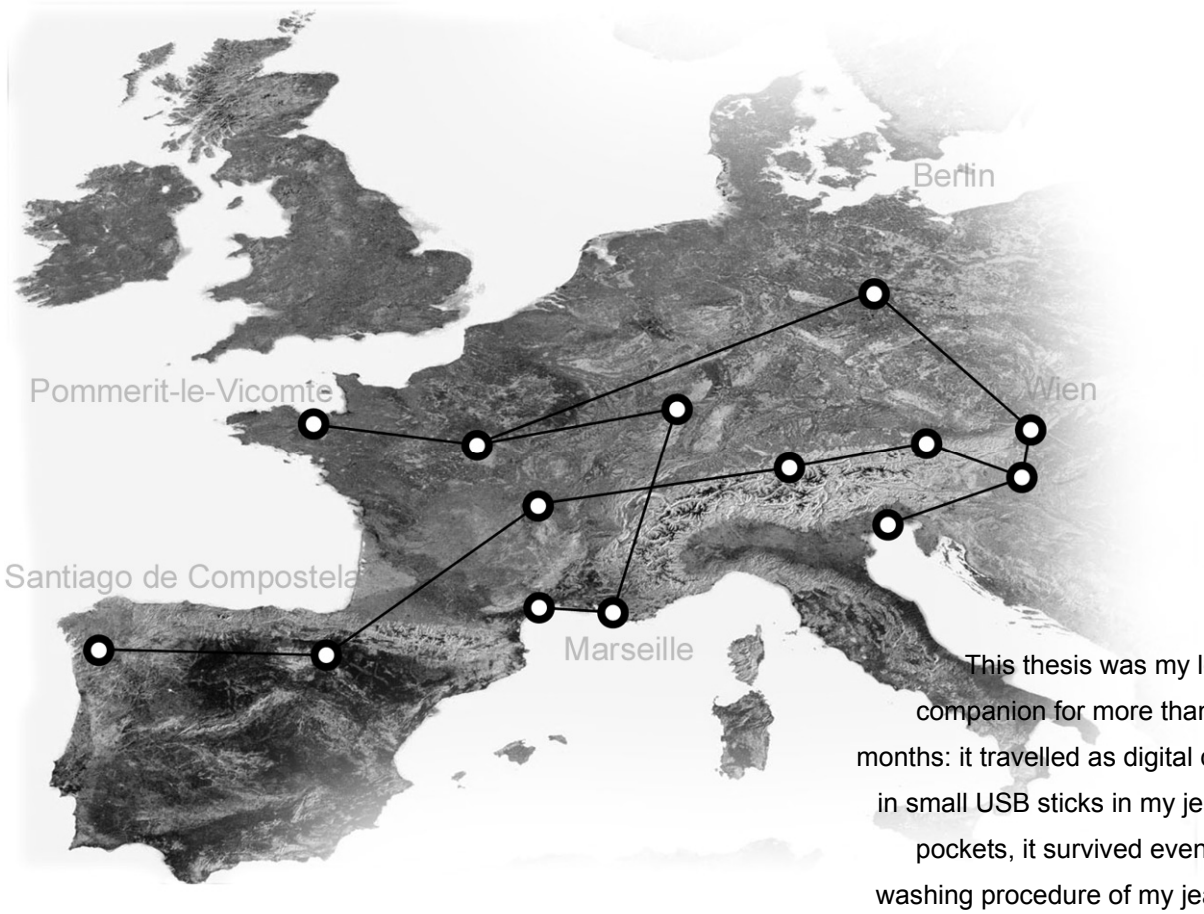
2 ACKNOWLEDGEMENTS



This thesis was my loyal companion for more than six months: it travelled as digital data in small USB sticks in my jeans' pockets, it survived even the washing procedure of my jeans, as a printed draft it crossed Western Europe in a bicycle bag, it visited Berlin, Venice, Strasburg, Montpellier by train or by plane, as shown in the satellite image above.

I would like to say thanks to all the people who helped me in the accomplishment of the present thesis: for their advices in scientific, mathematical or linguistic respect, for the measurements they performed (special thanks to the nurse staff!!) and for their affection which made it easy to overcome occasional difficulties.

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4 ABBREVIATIONS

ANP	atrial natriuretic peptide
AUC	area under the curve
BCM	*Body Composition Monitor*
BNP	brain natriuretic peptide
cf.	*confer*
CNP	C-type natriuretic peptide
CPR	Cardiopulmonary recirculation
e.g.	*exempli gratia*
EDTA	ethylenediaminetetraacetic acid
et al.	*et alii*
etc.	*et cetera*
GFR	glomerular filtration rate
HD	haemodialysis
i.e.	*id est*
n	number
NT-pro BNP	N-terminal piece of pro brain natriuretic peptide
p	probability value
r	correlation coefficient
vs.	*versus*

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7 ZUSAMMENFASSUNG

Einleitung: Hämodialyse ist nach wie vor mit einer hohen kardiovaskulären Mortalität vergesellschaftet. Ein wesentlicher Risikofaktor hierfür ist die chronische Expansion des Extrazellulärvolumens, deren Einschätzung in der Praxis schwierig ist. Es besteht daher großes Interesse an objektiven und gleichzeitig nicht-invasiven Messmethoden wie etwa der Bioimpedanz. Die zentrale Fragestellung dieser Arbeit war der Vergleich der Abschätzung des Volumenüberschusses nach klinischen Gesichtspunkten einerseits und nach biophysikalisch ermittelten Daten andererseits.

Methoden: Vor der Dialysebehandlung erfolgte die Bestimmung von extrazellulärem Volumen (V_{ECW}) und Volumenüberschuss (V_O) mittels einer Bioimpedanzspektroskopie-Methode (*Body Composition Monitor*, *Fresenius Medical Care*, Bad Homburg, Deutschland). Ausschlusskriterien waren implantierter Defibrillator oder Schrittmacher, Amputationen sowie lokale Ödeme. Andere erhobene Volumenindikatoren waren ein klinischer Score nach *Wizemann* sowie prä- und postdialytisches NT-pro BNP (C_{BNP_pre}, C_{BNP_post}). Das tatsächliche Ultrafiltrationsvolumen (V_{UF}) richtete sich nach dem gewohnten klinischen Trockengewicht und nicht nach den für die Studie erhobenen Volumenindikatoren.

Ergebnisse: Es wurden achtundzwanzig stabile, ambulante, chronische Hämodialysepatienten (darunter elf Frauen) aus dem Dialyseprogramm der Universitätsklinik Graz vermessen. Bei einem V_{ECW} von 17.9±3.5 [L] war das V_O im Mittel 2.1±1.5 [L]. Im Vergleich dazu war das V_{UF} 2.4±1.0 [L]. Es gab keinen signifikanten Zusammenhang zwischen V_O und V_{UF} (r=-0.145, p=0.461). Die Volumenindikatoren zu Dialysebeginn korrelierten großteils miteinander, C_{BNP_pre} korrelierte etwa positiv mit dem relativen Volumenüberschuss (=V_O/V_{ECW}) (r=0.581, p=0.001).

Diskussion und Schlussfolgerung: Die starke Übereinstimmung zwischen den einzelnen Volumenindikatoren zu Dialysebeginn spricht für deren Richtigkeit. Jedoch gab es eine große Diskrepanz zwischen diesen Volumenindikatoren und der tatsächlichen Ultrafiltrationsmenge (V_{UF}). Erklärungen hierfür (Fehler der „objektiven“ Messgrößen oder des klinischen Trockengewichts, korrekte Volumentherapie verunmöglicht durch Komorbidität etc.) konnten weder eindeutig bewiesen noch widerlegt werden.

8 ABSTRACT

Introduction: Haemodialysis is still associated to a high cardiovascular mortality. An important risk factor is the chronic expansion of the extracellular compartment, which is difficult to assess in clinical practice. This explains the interest in objective and, at the same time, non-invasive measurement methods such as bioimpedance analysis. The central aim in the present paper was the comparison of different volume assessment methods: assessment by clinical signs or by biophysical data.

Methods: Before dialysis treatment, extracellular volume (V_{ECW}) and volume overload (V_O) were assessed by a bioimpedance spectroscopy method (*Body Composition Monitor*, *Fresenius Medical Care*, Bad Homburg, Germany). Exclusion criteria were implanted pacemakers or defibrillators, amputations, as well as local œdema. Further volume indicators assessed were a clinical score, modified from *Wizemann*, and pre- and postdialytic NT-pro BNP (C_{BNP_pre}, C_{BNP_post}). The effective ultrafiltration volume (V_{UF}) corresponded to the habitual dry weight and not to the volume indicators assessed for the study.

Results: Measurements were performed in twenty-eight stable, chronic haemodialysis patients (eleven females) from the dialysis programme of the Graz Medical University. Mean V_{ECW} was 17.9±3.5 [L] and mean V_O 2.1±1.5 [L]: By comparison, V_{UF} was 2.4±1.0 [L]. There was no significant relationship between V_O and V_{UF} (r=-0.145, p=0.461). The volume indicators at the beginning of the treatment largely correlated with each other, C_{BNP_pre} was positively related to relative volume overload (=V_O/V_{ECW}) (r=0.581, p=0.001).

Discussion: The strong relationships found between the volume indicators at treatment beginning plead for their accuracy. However, the discrepancies between the volume indicators and the effective ultrafiltration volume were large. Explanations for this finding (inaccuracy of the “objective“ methods or of the clinical dry weight, accurate volume therapy impossible because of comorbidity) could neither be totally confirmed nor rejected.

9 INTRODUCTION

9.1 The Role of the Kidneys

The kidneys are involved in a multitude of physiological processes in the human body. Three major functions have been described: firstly, the kidneys excrete potentially toxic metabolites. Secondly, they regulate the volume and the osmolality of body fluids. Thirdly, they take part in the hormonal regulation by the release of erythropoietin, renin and 1.25 dihydrocholecalceferol. Volume regulation and the renin-angiotensin-aldosterone system have a strong impact on blood pressure. The present study was focussed on processes connected to volume regulation.

9.1.1 Volume Regulation as one Important Kidney Function

9.1.1.1 Normal Fluid Volumes and Osmolality

Approximately, two thirds of the adult body consist of water. The fluid volume in the cells is called intracellular compartment, which is normally greater than the fluid volume around the cells, the extracellular compartment. Blood volume can be considered either as a third small compartment or as parts of the two big compartments mentioned, intracellular and extracellular volume: plasma volume corresponds to the extracellular component of blood volume and blood cell volume to its intracellular component (Fig 14 on page 39).

Since water passes freely through the cell membranes, it shifts from one compartment to another as long as their osmolalities are different. The normal osmolality of body fluid is 280 [mosmol/L]. Total body mass of sodium determines total body water and hence extracellular water volume, if equal osmolality is assumed for intracellular and extracellular compartment. Intracellular water volume depends on blood sodium concentration, respectively on blood osmolality.

Fluid distribution is determined by the above mentioned osmolality as well as by other factors. There is a concept to describe and to merge all the factors, which is the compliance of a compartment. The compliance is the willingness of a compartment to accept an increase in volume (1) – this corresponds to the common idea of distensibility. Mathematically, compliance is defined as the change in volume at a given change in pressure.

9.1.1.2 Regulation Mechanisms

Regulation of body fluids can be divided into volume and osmolality regulation: the kidneys control the osmolality of the blood by adapting the osmolality in the urine (hypertonic or hypotonic urine), by adapting the levels of anti-diuretic hormone, also known as vasopressin. Another osmolality regulation mechanism is thirst, which protects against hyperosmolality.

Since the excretion of sodium by the kidneys is limited, salt intake has a major impact on total body sodium and hence on total body water. Important regulators of the renal excretion are the renin-angiotensin-aldosterone system, natriuretic peptides and blood pressure. Blood volume expansion increases blood pressure and glomerular filtration rate and thus natriuresis.

9.2 Fluid Retention

9.2.1 Results of Fluid Retention

Blood volume increases with an expansion of the extracellular compartment. As the venous system has the highest compliance, it is the first to increase. More fluid volume will return to the heart and thus diastolic filling volume will become greater, dilating the ventricles, whose walls thicken to protect themselves (*excentric hypertrophy*). Increased cardiac preload leads to increased cardiac afterload. Blood pressure increases in the arterial system as well (*arterial hypertension*).

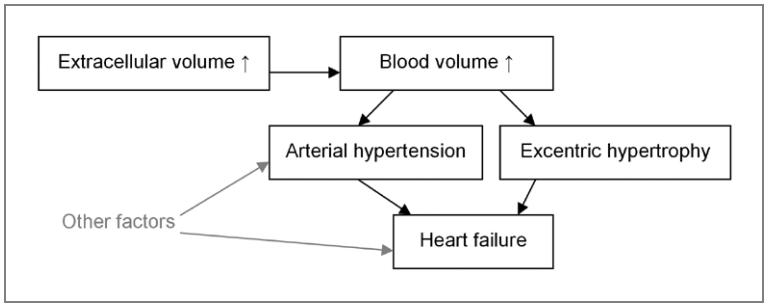

Fig 1 Pathophysiological consequences of volume overload
Figure modified from Mees (1)

Left ventricular hypertrophy and arterial hypertension are well-known cardiovascular risk factors, which contribute to a highly elevated cardiovascular death rate in dialysis population, reported to be up to forty times higher than in general population (2,3). Similarly, more advanced stages of chronic kidney disease “are associated with a greater burden of cardiovascular disease” (4).

9.2.2 The Dry Weight Concept

The therapy targets in end-stage renal disease can be deduced from the main functions of the kidneys, as described in chapter 9.1. Toxic metabolites are eliminated by dialysis itself. Dialysis treatment is usually combined with ultrafiltration, which means removal of fluid volume. The loss in hormonal function is replaced by medication, such as artificial erythropoietin. The clearance and distribution volume of toxic substances could be explained by the *kt/V Concept*. The *kt/V Concept* was without doubt an important progress to understand renal replacement therapy, but its dominating role concealed other treatment targets as volume removal. More and more, researchers and physicians became aware of the high cardiovascular mortality in dialysis patients and the role, volume overload plays in it (*cf.* previous chapter). These observations brought the *Dry Weight Concept* into focus.

Different definitions of dry weight have been proposed: according to *Mees*, dry weight corresponds to the weight a patient has when all body fluids are normal (1). Dry weight has also been defined “as that weight at the end of a dialysis treatment below which the patient, more often than not, will develop symptoms of hypotension” (5). A similar but more exact definition has been given by *Kuhlmann et al.*: dry weight is equal to that “posthemodialysis weight at which the patient is as close as possible to a normal hydration state without experiencing symptoms indicative of over or underhydration at or after the end of hemodialysis treatment” (6).

Please consider that the pathophysiological agent corresponds to volume (blood volume increase). Voume and mass are related by density, and since the density of water and tissues (apart from bone tissue) is close to unity (1 kg/L), the measurement of volume is conveniently replaced by the measure of mass. Weight, however, is equal to a force exerted by gravitation but not to mass nor to volume. The term “weight” thus has to be avoided and strictly speaking, *Dry Mass Concept* is the correct expression.

As the body mass of HD patients varies highly over the dialysis cycle, it is inevitable that a definition of dry mass includes a time scale. A dialysis cycle consists of the treatment period and the period till the next treamtent. The majority of authors propose that the body mass at the end of the ultrafiltration be considered as the reference mass, neglecting the differences in interdialytic mass gain: mass gain can be more or less rapid, depending on the salt intake and on the residual renal capacity of the patient (different generation and accumulation rates). Mass gain depends furthermore on the duration of the period between the ultrafiltration treatments (different interdialytic intervals). The shorter the interdialytic interval is, the smaller the interdialytic mass gain will be. In Fig 2, the generation/accumulation rate corresponds to the slope of the line and the interdialytic interval to the x-axis.

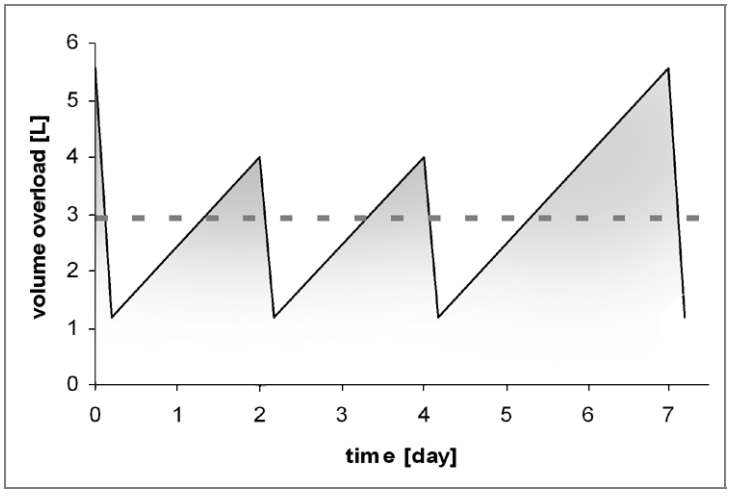

Fig 2 Schematic week profile of volume overload variation in haemodialysis patients
The dashed line is the mean volume overload over the three cycles.

For a correct reflection of body weight variations, the time scale of dry mass has to include the whole cycle. The author of the present paper proposes to define dry mass as that mean body mass over one

or more dialysis cycles at which the body fluid volumes are equal to those of a reference subject. The reference subject has to be healthy but all other properties (age, body tissue composition,...) have to comply with the actually measured subject.

Another argument for an extensive time scale of dry mass is given by clinical observations: cardiovascular mortality seems to be a function of the volume state not only at a given point of a time but of the volume state over the whole dialysis cycle. Cardiovascular mortality is not only linked to postdialytic volume overload (7) but also to interdialytic mass gain (8) and to predialytic volume overload (7).

However, the determination of body mass or body fluid volumes is not continuous but intermittent for practical reasons. The question is, at which frequency and at which points of time measurements have to be done, so that intermittent methods accurately reflect a continuous process.

9.2.3 Evaluation of Volume Overload

9.2.3.1 General Remarks

The importance of the volume overload is in contrast to the insufficiency of its measurement. Clinical signs found on examination or through the anamnesis are unspecific and insensitive, as they are only present in severe cases of volume disorders. Consequently, researchers have tried to find new parameters. There are totally diverse methods of measuring these parameters: ultrasound (*vena cava diameter*), biochemical analysis (*natriuretic peptides plasma levels*), application of alternating current (*bioimpedance*) and dilution methods (*dilution of bromide, deuterium,...*). Two of the methods enumerated will be discussed in greater detail, as they were central to the conducted study:

9.2.3.2 Natriuretic Peptides

The natriuretic peptide family comprises three structurally related peptide hormones: atrial natriuretic peptide, brain natriuretic peptide and C-type natriuretic peptide. They are commonly known under their abbreviations ANP, BNP respectively CNP.

The release of natriuretic peptides is proportional to cardiac distension through pressure and volume strain, endothelin and angiotensin II increase and sympathetic stimulation via beta-adrenoceptors (9). Natriuretic peptides are primarily synthesised in the heart and in other organs such as the brain. There are precursor molecules, *e.g.* pro BNP (108 amino acids), which is cleaved in BNP (32 amino acids) and the N-terminal piece of BNP also known as NT-pro BNP (76 amino acids). Natriuretic peptides are degraded by neutral endopeptidase. Renal excretion is high for NT-pro BNP and low for BNP.

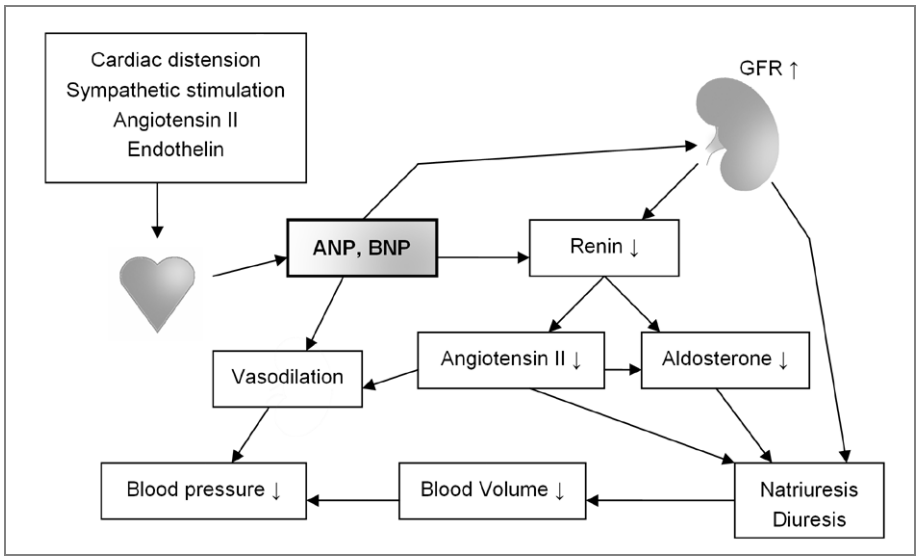

Fig 3 Stimuli and effectors of natriuretic peptides
Figure modified from (9)

Natriuretic peptides are involved in the regulation of the cardiovascular and the renal system: the glomerular filtration rate and the filtration fraction is influenced by BNP and ANP plasma levels: they increase fluid excretion (diuresis) and sodium excretion (natriuresis). They inhibit renin release in the kidneys, which down-regulates the whole renin-angiotensin-aldosterone cascade. Furthermore, natriuretic peptides induce a dilatation of the venous and the arterial vessels.

Taken together, natriuretic peptides decrease blood volume, cardiac pre- and afterload and pressure in both - arterial and venous - systems. In short, natriuretic peptides antagonize not only the release but also the action of the renin-angiotensin-aldosterone system.

With its long half-life, the NT-pro BNP molecule is the most important natriuretic peptide in clinical practice. NT-pro BNP is used in the assessment of cardiac impairment. The observation that NT-pro BNP was highly elevated in end-stage renal disease, turned it into a marker for volume state.

9.2.3.3 Bioimpedance

9.2.3.3.1 General Concept

The interaction between electric current and biological tissues was already observed by *Galvani* in the 18th century. Biological tissues conduct electricity because charged particles (electrolytes) are dissolved in water. While the concentration of electrolytes is controlled to cover a narrow range, the amount of water shows much larger variation. The electrical conductivity of a tissue therefore is assumed to reflect the volume of the electrolyte solution. Not all biological tissues conduct the current to the same degree; the conductivity, and the resistance as the inverse of the conductivity, depend on the electric property of the respective tissue. The resistance of a tissue unit - with a cross-sectional area of 1 [cm^2] and a length of 1 [cm] - is called *resistivity* (ρ). In applying an alternating current instead of continuous current, the concept of resistance has to be extended to *impedance* (*Z*). The

inverse of impedance is *admittance*. Impedance is a complex number with a real part (*resistance*) and an imaginary part (*reactance*).

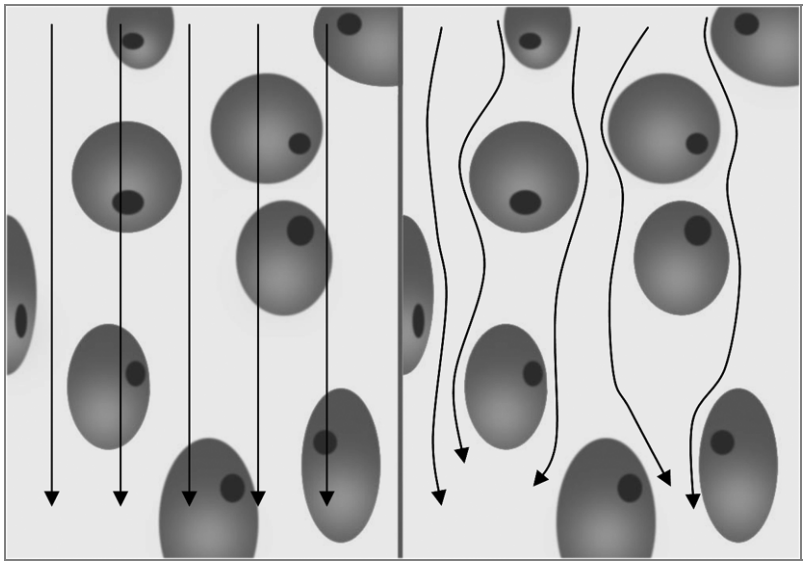

Fig 4 Current distribution at different frequencies
Distribution at infinitely high frequency is depicted on the left and that at infinitely low frequency on the right.

On the cellular level, the two important elements of bioimpedance are body fluid and cell membranes. Body fluid is distributed around the cells (*extracellular compartment*) and in the cells (*intracellular compartment*). Body fluid is a conductive suspension of water and solids, such as ions. Body fluid - regardless whether extracellular or intracellular - is consequently considered to be a purely resistive medium. Biological cell membranes can be compared to capacitors, and their electrical effect is equal to reactance: at zero frequency, which is equal to direct current, the cell membrane behaves as isolator and the current passes only through the fluid around the cells, in other words, through the extracellular compartment. In this case, impedance is purely resistive and a function of the size of the extracellular compartment (10). With alternating current, the cell membrane gets charged and discharged at the rate of the frequency applied and the electrical effects are transmitted into the cell. Hence, the higher the frequency, the larger is the part of the intracellular compartment, which is measured. At infinitely high frequency, the charge and discharge of the cell membrane happens so fast that the reactance as an effect of the cell membrane becomes zero – the cell membrane behaves as a conductor. The current passes in equal measure through both compartments, extracellular and intracellular. At a characteristic frequency, the reactance as an effect of the cell membrane reaches its maximum (10).

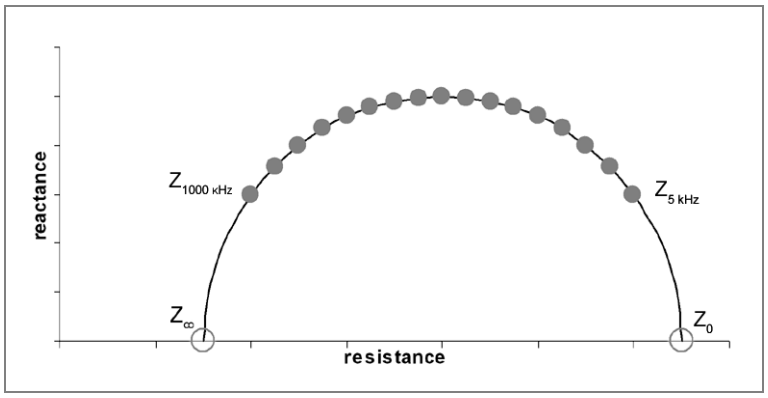

Fig 5 Resistance-reactance relationship at different frequencies
The full grey dots represent impedance values (Z) measured for a range of frequencies (5 to 1000 kHz). The black line shows the assumed semi-circle of impedance for a continuous range of frequencies. The big open dots represent the resistance of infinitely low (Z_0) or high frequency (Z_∞).

In effect, infinitely high and low frequencies cannot be applied for both technical and theoretical reasons. Bioimpedance spectroscopy measures impedance at a wide range of frequencies between low and high frequencies. In depicting these measurement data in a resistance-reactance plot, the data values can be connected to yield a curve (Fig 5). This curve corresponds to a semi-circle, which is opened towards negative reactance values and has been described in the *Cole Model* (11,12). By extrapolating the curve, two intersection points with the resistance axis are obtained. These points correspond to the resistance values of infinitely low respectively high frequency. These two resistance values can be related to extracellular and total body fluid volume, as demonstrated above. Intracellular volume is the result of subtracting extracellular volume from total body fluid volume.

Additional theoretical background was given by *Hanai's Mixture Theory* (13), which describes the effect on conductivity in a suspension of non-conductive and conductive mediums. *Hanai* postulated that this theory was valid in mediums with non-conductive concentrations between 10 and 90 [%] (10). In application of the *Hanai Theory* to bioimpedance, the extracellular compartment is such a medium at low frequency and total body fluid at high frequency.

9.2.3.3.2 Conductor Geometry

Bioimpedance models simplify the complex geometry of the human body. The body segments are considered as cylindrical conductors. The equation for the electrical resistance in a cylinder is well-known: The electrical resistance (R) of a cylinder is proportional to the length (L) of the cylinder and indirect proportional to the cross-sectional area (A) of the cylinder. ρ is the resistivity of the respective tissue.

$$R = \rho \frac{L}{A}$$

Eq 1 Resistance in a cylinder

Expanding the fraction in Eq 1 by *L* and rearranging gives an expression for volume in terms of *R*, *L*, and *ρ*:

$$V = \rho \frac{L^2}{R}$$

Eq 2 Volume expressed by resistance, length and resistivity

Consequently, length as well as specific resistivity are crucial parameters for bioimpedance equations. These considerations, which are valid in the simple geometry of a cylinder, have been transferred to the complex geometry of the human body by means of certain algorithms (*shape factors*). Shape factors are based on the observation that most people appear to have certain distribution of diameters in the different body segments.

9.2.3.3.3 Different Concepts

A large variety of bioimpedance methods has been proposed. They can be classified by the number and range of frequencies applied and by the body part measured. The bioengineering market offers single-frequency, dual-frequency and (fixed and variable) multi-frequency devices. The method of variable multi-frequency is commonly known as bioimpedance spectroscopy and is the sole method, whose equations are not empirically derived, but through modelling. These models are, to various degrees, rather descriptive or rather explanatory. Bioimpedance is always measured in a segment of the body, and total body impedance is only extrapolated by the segment impedance. Positions of electrodes described in literature are wrist-to-ankle, leg-to-leg, arm-to-arm, elbow-to-knee,... There is one rule that applies to all these methods: the smaller the measured body segment, the more uniform the segment will be, but the harder it will be to relate the segment to the total body.

9.3 Influence of Fluid Volume State on Cardiac System

The complexity of the relations between fluid volumes and the cardiac system and the importance of the kidneys in controlling volume output and blood pressure was shown by *Guyton* (14). *Guyton* assembled the main factors of body fluid and pressure control into one single control loop, depicted in Fig 6. Extracellular volume and its excess, in other words volume overload, determine blood volume. Blood volume influences mean circulatory filling pressure, which determines right atrial pressure (preload). *Starling's Law* postulates that high preload leads to high afterload: Right atrial pressure controls diastolic filling and hence cardiac output. Most relationships are non-linear. Furthermore, these relationships are defined for the equilibrated state, while the state during and at the end of dialysis is far from equilibrium.

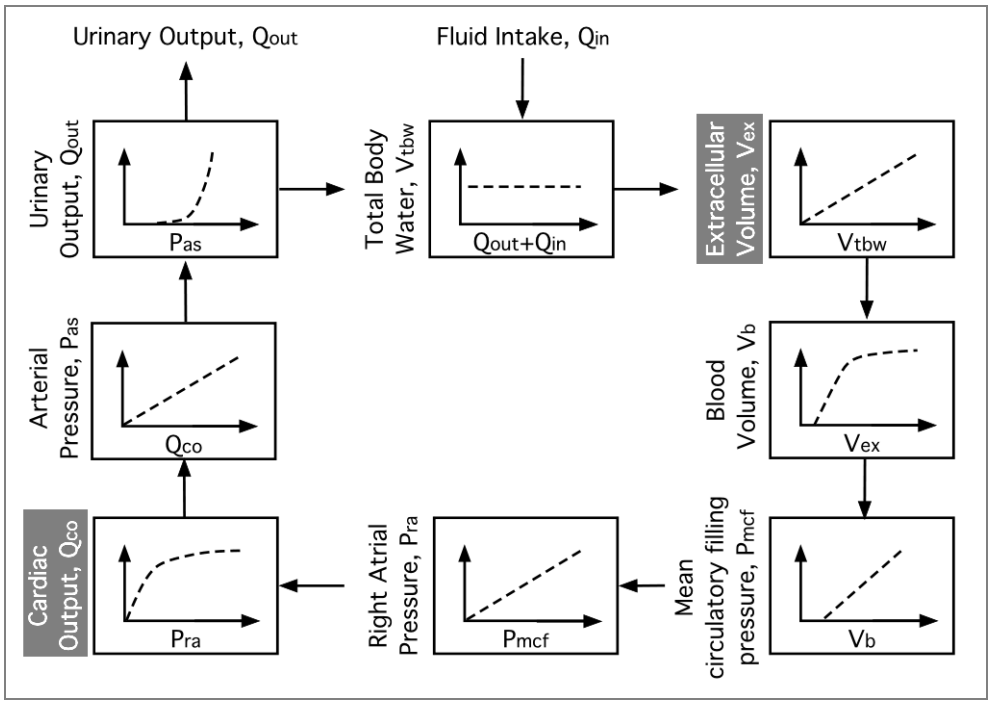

Fig 6 Guyton's physiology of volume state and cardiac function
The full names of the abbreviated parameters are given in the vertical captions.

To go back to blood volume - the relevant fluid volume - it is a part of extracellular volume. Thus blood volume increases with an expansion of the extracellular compartment, but only slowly above a certain amount, estimated to be five litres by *Mees* (1). This non-linear relationship between blood volume and the second subcompartment of extracellular volume, interstitial volume, depends on interstitial and intracapillary pressures. Equilibrium is only established if fluid volume remains unchanged during a certain period. In other words, extracellular volume reflects blood volume only in the steady state. Important to note, variations in the blood-to-extracellular-volume curve are observed between individuals. Thus, it is not possible to calculate one of the two absolute volumes by the other, even if extracellular volume reflects blood volume.

9.4 Statement of the Problem, Aims and Hypothesis

The aims of the present study were to compare clinical and biophysical assessment methods of volume state and to investigate the relation of volume state to cardiac parameters. The exact questions and the chapters, in which the respective question is discussed, are given below.

1) How to characterise the participants?
   chapter 11.1, 12.1

2) Volume indicators: Which volume indicators were investigated? How can they be described? By which other factors were they influenced?
   chapter 11.2, 12.2

3) Did the different volume indicators correlate?
   chapter 11.3, 12.3

4) Did ultrafiltration volume correspond to the following values: (4a) to the change of volume indicators? (4b) to predialytic volume indicators?
   chapter 11.4, 12.4

5) In case of differences between predialytic volume indicators and ultrafiltration volume: can these observed differences be explained by other factors?
   chapter 11.5, 12.5

6) Was there a relationship between cardiac output and volume state? Which other factors influence cardiac output? Did peripheral resistance depend on volume overload?
   chapter 11.6, 12.6

7) How can body tissue composition be evaluated (lean and adipose tissue mass)? Did the tissue composition confound volume-overload equations?
   chapter 11.7, 12.7

8) Follow-up: Did values change over the time? Were the weight changes reflected by changes of bioimpedance values?
   chapter 11.8, 12.8

9) What are the fundamental conclusions from the present study? What are its limitations?
   chapter 12.9

10 MATERIAL AND METHODS

10.1 Patients

Patients were recruited from the dialysis unit of the Graz University Hospital (Auenbruggerplatz 27, 8036 Graz, Austria). Approval was abtained from the ethical board of the Medical University of Graz. All participants gave their informed consent to the study.

The inclusion criteria were clinical stable state and chronic haemodialysis treatment. Exclusion criteria were only due to technical reasons determined by bioimpedance spectroscopy. Patients who had pacemakers or implantable cardioverter-defibrillators were excluded. Bioimpedance measurement and the pacemakers are both based on the application of electrical current and pulses with a potential risk of interference. Amputation reduces the length of the limbs and consequently reduces the overall electric resistance measured by bioimpedance, since resistance is proportional to resistivity and to length and inversely proportional to cross-sectional area. In case of unilateral amputation (*e.g.* of the left leg), it has been proposed to measure the intact side (in this example, between right wrist and right ankles). In this case, overall length is not altered, but body mass is altered, which is another crucial parameter for bioimpedance equations. Since the estimation of mass loss may be not sufficiently exact, it was chosen to exclude not only patients with bilateral amputations but also those with unilateral amputation. The third exclusion criterion was the bilateral presence of œdema which were due, however, to local affections and not to volume overload. To give an example, a male patient had to be excluded whose swollen right leg was caused by lymphœdema and whose œdema on the left hand was a consequence of a non treated fracture.

Measurement of cardiac output and access flow by saline dilution using ultrasonic detection was only possible in patients with a peripheral arterio-venous access (twenty-three out of twenty-eight; fifteen males and eight females). The remaining five patients had a central venous access.

10.2 Study Protocol

10.2.1 General Remarks

The study was structured as a cross-sectional study. In addition, some patients had a follow-up, consisting of a second measurement. Every measurement was performed at mid-week dialysis sessions, in order to avoid weekly variations in fluid status: on Wednesday for those on a Monday-Wednesday-Friday schedule and on Thursday for those on a Tuesday-Thursday-Saturday schedule. All measurements including the follow-up measurements were carried out within six weeks, from April 22th to June 3rd 2009.

Predialytic measurements, which took between twenty and thirty minutes, comprised acquisition of anthropometric and bioimpedance data, clinical examination, blood pressure measurement and taking

answers for the questionnaires. All these measurements were done by the same investigator (the author) before dialysis, in a separate room of the dialysis unit. Thereafter, the participants underwent their standard ultrafiltration and haemodialysis treatment. The nurse staff of the dialysis unit, used to the handling of the saline dilution method, performed intradialytic measurements of cardic output and access flow. Moreover, blood samples were taken by the nurse staff at the beginning and at the end of the HD treatment.

Data acquisition was standardized by a case report (attached in the Appendix). Apart from single-use material, the same devices were used for all measurements.

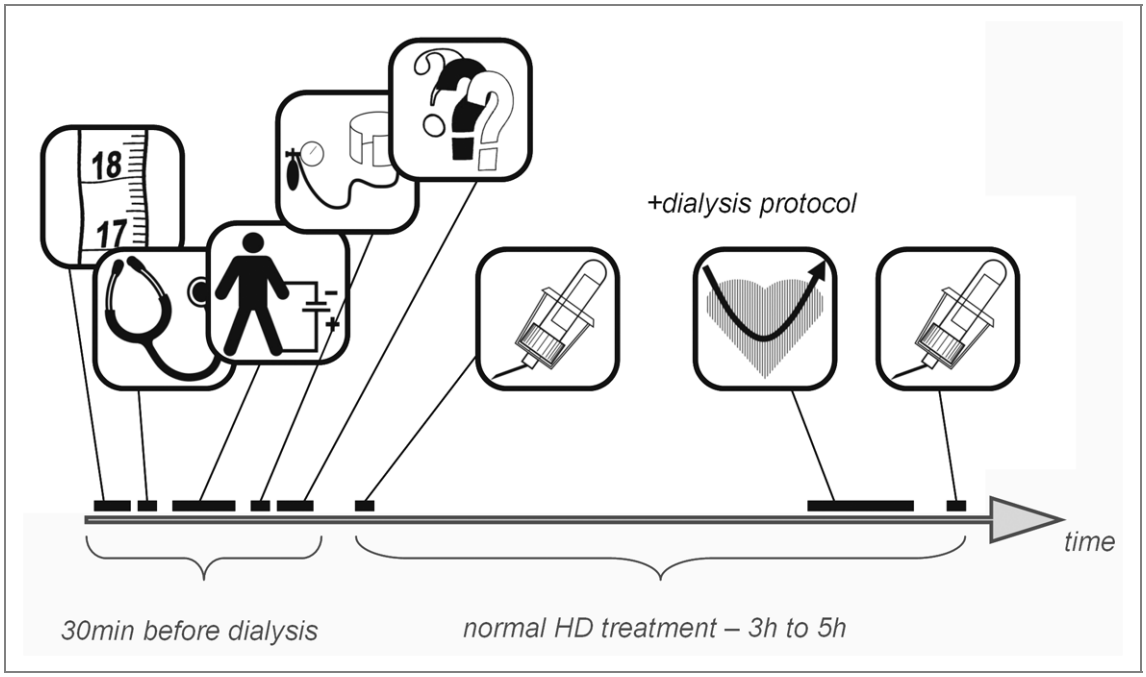

Fig 7 Measurements, put in chronological order

A brief overview of the measurements and values obtained is shown in Fig 7 and in Tab 10-1. In Fig 7 the items are arranged in chronological order, whereas assembles the items regarding content. In the latter, measurements or values are merged into the respective system that they investigate.

Tab 10-1 Measurements and values

Volume Indicators	Cardiac Parameters	Nutritional Evaluation
 Bioimpedance *Water volumes*	 Saline dilution *Cardiac output, access flow*	 Anthropometry *Body mass index,...*
 Laboratory NT-pro BNP	 Laboratory NT-pro BNP	 Laboratory *Lipid profile, albumin,...*
 Blood pressure	 Blood pressure	 Bioimpedance *Tissue masses*
 Antihypertensives, clinical volume score		
 Short clinical examination		
 Anthropometry *Watson,...*		

10.2.2 Predialytic Measurements

10.2.2.1 General Data

Measurements were identified by a five digit code, abbreviated N_{ID}. Digits one and two were assigned to the first measurement of each patient, running from 01, digits three and four encoded the first, respectively last name of the patient and digit five was used to encode successive measurements taken from the same patient. N_{ID} does not render patient data totally anonymous.

The integer T_{age} was displayed in [years]. For subjects in the 23rd life year, T_{age} was counted as 22, for subjects in the 24th life year, T_{age} was counted as 23, and so on. Two dichotomous values were recorded as well: gender (N_{sex}) was either male or female [M/F]. Subjects were asked whether they were diabetics or not. If so, N_{diab} became Y. Otherwise, N_{diab} became N. Date of measurements (T_{date}) was an additional part of these general data. It was conform to the example “22-Apr-2009”.

10.2.2.2 Anthropometric Measurements

10.2.2.2.1 Weight

Predialytic body mass was measured by an automatic electronic scale from *Terraillon France* (B.P. 73, 78403 Chatou Cedex, France). This product is accredited to measurements up to 150 kilogrammes. The subjects were asked to put off all objects (watch, pair of glasses,...) and to get undressed except for underwear and a shirt. Erect posture during weighing was demanded. Furthermore, patients were told to stand still, arms hanging loosely at their sides and not to look down but forward. The unit for all mass values was [kg]. M_{pre} was recorded to the nearest 0.1 kilogramme. For M_{pre} and all following variables, the level of measurement was ratio scale (15), unless mentioned otherwise.

10.2.2.2.2 Height

To determine body height (L_{height}), we used a measurement rod, *The Leicester Height Measure* from *Tanita Corporation* (14-2, 1-Chome, Maeno-Cho, Itabashi-Ku, Tokyo, Japan). Patients were instructed to stand with their flat feet on the centre of the base plate, feet together, heels against the ruler. They should stretch to their fullest height with the head facing forward, so that the Frankfort plane became horizontal. “The Frankfort plane is an imaginary line passing through the external ear canal and across the top of the lower bone of the eye socket, directly under the eye” (16). Body height and all the other anthropometric lengths that we will speak of, were recorded in metres [m] and measured to the nearest 10^{-3} [m], in other words, to the nearest millimetre.

10.2.2.2.3 Waist Circumference

For the measurement of waist circumference (L_{waist}), a tape was placed on a horizontal plane at the point midway between the lowest rib and the iliac crest. If a shirt was worn, it was lifted up. The patients, who were standing straight, were asked to reduce their respiration. The hip circumference (L_{hip}) was measured following a horizontal plane through the big trochanters.

10.2.2.2.4 Mid Upper Arm Circumference

Mid upper arm circumference (L_{MUAC}) was measured midway between the elbow and the acromion. It was taken on the same side as blood pressure to verify whether the blood pressure cuff was of appropriate size. Furthermore, mid upper arm circumference offers information about the nutritional status of the subject.

10.2.2.2.5 Calculated Values

Values derived from anthropometric measurements were body surface area estimated by *Du Bois Equation* (A_{BSA}) (17), body mass index (I_{BMI}), waist-to-hip ratio (I_{WHR}). Total body water volume was also estimated by a linear regression equation obtained by *Watson et al.* (18). The equation was derived from data of different studies (723 subjects in total), whose total body water volume was measusred by various dilution methods. For the equation of the values of this paragraph and of all other derived variables, please refer to Tab 13-2 on page B.

10.2.2.3 Clinical Examination

Clinical examination was short. It included auscultation of the lungs to detect bilateral moist râles (N_{moist}) as a central sign for volume overload. Œdema of the legs (N_{edema}) were specified either as bilateral œdema of the ankles or as bilateral pretibial œdema. Both variables had dichotomous values (Y/N). N indicated the total absence of the signs, described above. Y indicated the presence of these symptoms, regardless whether symptoms were pronounced or not.

10.2.2.4 Blood Pressure

Evaluation of blood pressure was done at rest after two minutes in supine position. If the subject had an arterio-venous access, blood pressure was taken on the opposite side. If blood pressure values were doubtful, the measurement was repeated after another three minutes. In this case, the first blood pressure measurement was rejected and the second was recorded. A non-invasive oscillometric cuff method was used, offered by the *CBM-7000* from *Colin Corporation* (2007-1 Hayashi, Komaki, Aichi 485-8501, Japan). With this method, systolic and diastolic pressures are derived from the magnitude and shape of pressure oscillations measured in the cuff during cuff deflation by proprietary algorithms. The cuff used had a bladder width of 12 [cm], appropriate for patients with arm circumference from 23 to 33 [cm]. The *CBM-7000* provides a second method enabling continuous blood pressure monitoring by tonometry. This second method was not employed for practical reasons and for patient comfort. The measured values were predialytic systolic blood pressure (P_{sys_pre}), predialytic diastolic blood pressure (P_{dia_pre}) and predialytic heart rate (F_{pre}). Derived values were predialytic mean arterial pressure (P_{mean_pre}) and predialytic pulse pressure (P_{pulse_pre}).

10.2.2.5 Bioimpedance

Bioimpedance allows identifying the volume of different body compartments. The device used was the *Body Composition Monitor* (*BCM*), a multi-frequency bioimpedance device from *Fresenius Medical Care* (Else-Kröner-Straße 1, 61352 Bad Homburg, Germany). It is a whole-body method, the proximal electrodes were placed on wrist and ankle of one side. Measurement was done after five minutes in supine position on a flat bed. Patients were allowed to have only one small head cushion. Patients were told to move as little as possible during the five minutes before measurement and to lie totally still during the measurement itself. The side of arterio-venous access or of central venous access was avoided, except that a local œdema on the access-free side forced measurement on the access side. The variable N_{side} encoded the side of the measurement: firstly, whether it was the left or right side; secondly, whether it was the access or access-free side.

The following values were obtained directly by the *Body Composition Monitor* (*BCM*): total body water volume (V_{tot}) is the sum of extracellular water volume (V_{ECW}) and intracellular water volume (V_{ICW}). The innovation compared to other bioimpedance methods is the quantification of volume overload (V_O) in [L]. The scientific basis is a three-compartment model, developed by *Chamney et al.* (19). Central to this model is the assumption that healthy tissues contain a fixed proportion of water volumes

("normally hydrated"). Hence, the ratio between extracellular and intracellular water volume ($I_{ECW/ICW}$) is also fixed in a tissue. The three compartments are:

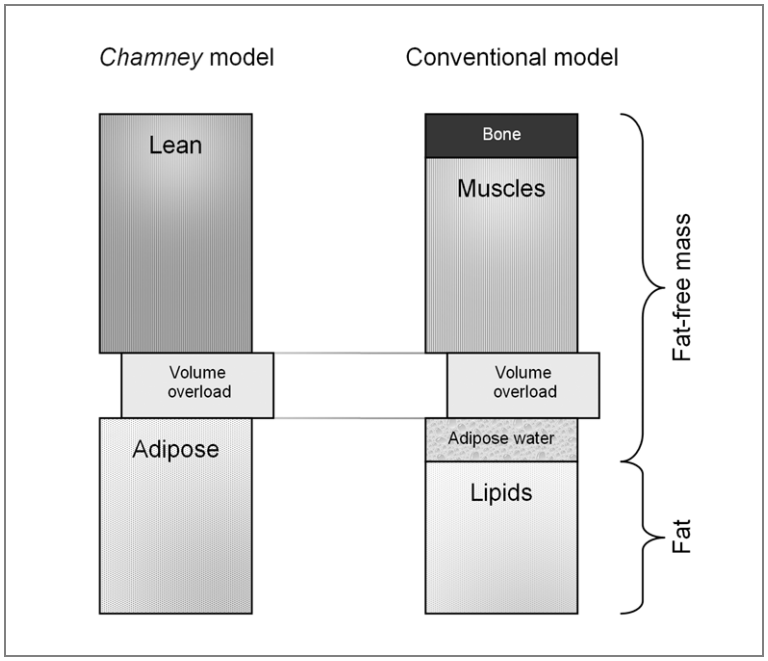

Fig 8 Compartments in bioimpedance models
Figure modified from (19)

1) Lean tissue mass (M_{LTM}) contains water, protein, osseous and non-osseous minerals and essential lipids with some intracellular lipids. The ratio of bone mineral to total protein is considered to be constant. Lean tissue mass is equal to fat-free mass in conventional models but without volume overload and without adipose water. In this model, extracellular and intracellular water volumes and body mass are the only input variables to calculate lean tissue mass.

2) Adipose tissue mass (M_{ATM}) consists of stored lipids, essential lipids, adipose water volume and solids (proteins and non-osseous minerals). It corresponds to fat mass in conventional models but unlike them includes the adipose water volume. Calculation of adipose tissue mass is similar to that of lean tissue mass.

3) Volume overload (V_O) is considered to be strictly extracellular, which is correct if osmolality is within its normal range. The sum of the extracellular water volumes of the two tissues provides a volume reference, against which overload of water volume can be identified. The equation given below from *Chamney's* study is simplified, neglecting that extracellular fluid is a solution containing water and to a minor degree solids. The water fraction of extracellular fluid is 0.98 (20). Thus, water volume overload has to be corrected by this factor of 0.98 to obtain fluid volume overload. In the equation given below, I_{ECW_LTM} and I_{ECW_ATM} represent the extracellular water volume fractions of lean tissue mass and of adipose tissue mass, V_{ECW} is the extracellular volume.

$$V_O \approx V_{ECW} - (M_{LTM} \cdot I_{ECW\_LTM} + M_{ATM} \cdot I_{ECW\_ATM})$$

Eq 3 Simplified calculation of volume overload

Since the terminology is not consistent in litterature, the terms used in different papers are given in Tab 10-2. In the present paper, V_O is called V_{O_pre} in the result and discussion chapter, since volume overload was measured before dialysis in the present study.

Tab 10-2 Different terms for the three compartments

Commercial *BCM* Device		*Chamney et al.*		*Stockinger*	
Variable		Variable		Variable	
OH	Overhydration	ExF	Excess fluid	V_O	Volume overload
LTM	Lean tissue mass	NH_LT	Normally hydrated lean tissue	M_{LTM}	Lean tissue mass
ATM	Adipose tissue mass	NH_AT	Normally hydrated adipose tissue	M_{ATM}	Adipose tissue mass

Chamney et al. conducted a study in order to quantify water volume fractions of Eq 3 (19). In 104 healthy subjects, water volumes, namely extracellular and total body water volume, were determined by bromide and deuterium dilution methods. Total body fat was measured by dual-energy X-ray absorptiometry and other methods.

The measured total water volume fraction of lean tissue mass was 0.703±0.009 and the extracellular component was 0.266±0.007. In adipose tissue mass, total water volume fraction was 0.197±0.042 and extracellular water volume fraction was 0.127±0.015. As said above, lean tissue and adipose tissue mass can be expressed by extracellular and intracellular water volumes and body mass. Finally, the expression for volume overload may be reduced to the following as described in (19):

$$V_O = 1.136 \cdot V_{ECW} - 0.430 \cdot V_{ICW} - 0.114 \cdot M_{pre}$$

Eq 4 Quantification of volume overload

As we can see in Eq 4, there is no need for sex or age as input variables. The water volume fraction in women is smaller than in men, but this is likely to be due to differences in body composition (higher body fat percentage in women). The same consideration was proposed for age: the smaller water volume fraction in older patients may be simply a consequence of changed body composition.

Further values measured by the *Body Composition Monitor* were fat tissue mass (M_{FAT}) corresponding to adipose tissue mass without adipose water and body cell mass (M_{BCM}) which corresponded to the mass of cells with active metabolism.

The following values were calculated on the basis of the values cited above or of the input variables such as mass (M_{pre}): postdialytic volume overload (V_{O_post}), the ratio between extracellular water volume and intracellular water volume ($I_{ECW/ICW}$), relative fat tissue mass (I_{FAT}), fat tissue index (I_{FTI}), predialytic relative volume overload (I_{VO_pre}), postdialytic relative volume overload (I_{VO_post}).

Postdialytic volume overload (V_{O_post}) was calculated by subtracting ultrafiltration volume from predialytic volume overload. This is based on two assumptions: firstly, ultrafiltration treatment removes fluid strictly from the extracellular compartment. Secondly, body composition, in other words, fat and lean tissues, is not changed by a single dialysis session. Relative volumes were determined by comparing absolute volumes to extracellular water volume.

10.2.2.6 Questionnaires

10.2.2.6.1 Clinical Volume Score

This score, developed by *Wizemann* and *Shilling* (21), modified by *Kraemer* (22), systematically assesses clinical symptoms of volume state. Symptoms were weighted according to the severity of volume overload or depletion that they indicate. Patients were asked, whether they had regularly observed the symptoms since the last adaptation of dry mass. Negative points were attributed to symptoms of volume depletion, positive points to those of volume overload. For the exact score refer to Tab 10-3. If the questionnaire attributed points for the same symptom in various degrees (f.e. severe and mild cramps), for subjects presenting the severe form of the disease (severe cramps), only the points of the severe symptoms were taken into account. The sum of all points was expressed in the variable N_{score}. Symptoms of hypotension (N_{sympt2}, N_{sympt3}, N_{sympt8}) were merged to the variable $N_{hypotens}$ [0/1]. $N_{hypotens}$ was 1 for any symptom indicating hypotension, otherwise $N_{hypotens}$ = 0. Similarly, symptoms indicating fatigue (N_{sympt6}, N_{sympt7}) were merged into the variable $N_{fatigue}$ and symptoms indicating cramps (N_{sympt4}, N_{sympt5}) were merged into N_{cramps}.

Tab 10-3 Clinical score of volume state
Absence of symptoms given in this table was considered as normal volume state (=zero points)

	Symptoms of Hypovolemia			Symptoms of Hypervolemia	
N_{sympt1}	Thirst immediately after haemodialysis	-1	$N_{sympt10}$	Blood pressure increase during ultrafiltration	+2
N_{sympt2}	Sympt. hypotension, position change	-1	$N_{sympt11}$	Pretibial œdema, weak	+2
N_{sympt3}	Sympt. hypotension, requiring saline infusion	-2	$N_{sympt12}$	Chronic coughing	+2
N_{sympt4}	Muscle cramps, moderate (calf)	-2	$N_{sympt13}$	Dyspnoea at rest, recumbent	+2

N_{sympt5}	Muscle cramps, severe (calf)	-3	$N_{sympt14}$	Pretibial œdema, severe	+3
N_{sympt6}	Limpness/tiredness between dialyses	-3	$N_{sympt15}$	Dyspnoea at rest, one cushion	+3
N_{sympt7}	Dizziness between dialyses	-4	$N_{sympt16}$	Dyspnoea at rest, two cushions	+4
N_{sympt8}	Sympt. hypotension, vomiting	-6	$N_{sympt17}$	Dyspnoea at rest, sitting	+6

10.2.2.6.2 Antihypertensive Medication

Antihypertensive medication was first copied from the newest drug prescription in the patient file. This information was verified by asking the patient, which antihypertensives were taken to exclude a bias by non-compliance to drug prescription.

The generic names of the pharmacological substances were recorded. The total number of antihypertensive drugs was expressed in the variable N_{AHD}. In case of drugs consisting of more than one pharmacologically active substance, we counted it nevertheless as one drug. As the renal function was restricted in the participating patients, diuretics were not considered as antihypertensive drugs.

10.2.2.6.3 Residual Urine Volume

The patient file was scanned for the latest evaluation of residual urine volume, done by a physician. Subsequently, the patient was asked to estimate his residual urine volume to the nearest 0.25 litres. As the residual urine volume (V_{resid_urine}) was incompletely recorded in patient files, the information given by the patient was considered as correct.

10.2.3 Intradialytic Measurement

10.2.3.1 Laboratory Data

Blood samples were taken at the beginning and at the end of a given dialysis session. Predialytic blood samples were drawn immediately before ultrafiltration treatment directly from the dialysis needle, if the patient had an arterio-venous fistula. In patients with *vena cava* access blocked by heparin, blood was drawn directly from this access before the treatment started. If the *vena cava* access was blocked by sodium citrate, blood samples were obtained by the puncture of the haemodialysis machine's tube system, briefly after the start of ultrafiltration treatment. All postdialytic blood samples were taken from the dialysis machine, too, briefly before the end of the treatment. Blood samples were collected in lithium heparin vacuum tubes for NT-pro BNP, lipid profile, albumin and total protein. Through the predialytic blood samples, many values were obtained, whereas the only values of the samples after ultrafiltration treatment were the second values of NT-pro BNP and bicarbonate. The blood samples were sent to one of the central laboratories of the Graz University Hospital (Klinisches Institut für Medizinische und Chemische Labordiagnostik, Laborbereich 2, Auenbruggerplatz 15, 8036

Graz, Austria). NT-pro BNP, lipid profile and protein markers were all analysed by *MODULAR ANALYTICS EVO* from *F. Hoffmann-La Roche AG* (Grenzacherstrasse 124, CH-4070 Basel, Switzerland).

We derived the following values from the the pre- and postdialytic NT-pro BNP levels (C_{BNP_pre}, C_{BNP_post}): change between predialytic and postdialytic NT-pro BNP (C_{BNP_change}), relative change between predialytic and postdialytic NT-pro BNP (I_{BNP_change}), relative change between predialytic and postdialytic NT-pro BNP, at a given ultrafiltration volume ($I_{BNP\_change/UFV}$).

Patients were not fasting, that is why the results of lipid profile have to be questioned: total cholesterol (C_{chol}), low density lipoprotein (C_{LDL}), high density lipoprotein (C_{HDL}), triglyceride (C_{tri}) and as a derived value, the ratio low density lipoprotein/ high density lipoprotein ($I_{LDL/HDL}$). Other nutritional parameters were total protein ($C_{protein\_total}$), albumin (C_{alb}).

10.2.3.2 Dialysis Protocol

In daily routine, the nurse staff write their observations down in a standardized report, the dialysis protocol. These measurements were performed by different persons, it was even possible that a subject was measured by more than one person. On the other hand, the measurements were highly automatized so that reproducibility can be assumed. The following results were taken from the dialysis protocol:

10.2.3.2.1 Blood Pressures

Blood pressure was measured several times during the haemodialysis treatment with a measuring interval of one hour or less. Blood pressure devices, which were based on an oscillometric method, were integrated in the haemodialysis machines (*AK 200 S* and *AK 200 Ultra S* from *Gambro AB* and *4008 H*, *5008 H* from *Fresenius Medical Care*).

The values of the first measure may serve as an example: the time of the 1st intradialytic blood pressure measurement (T_{P1}), 1st intradialytic systolic blood pressure (P_{sys1}), 1st intradialytic diastolic blood pressure (P_{dia1}), 1st intradialytic heart rate (F_1). The last measure was recorded as eighth measurement, no matter if it was the eighth measurement in this patient or not (T_{P8}, P_{sys8}, P_{dia8}, F_8). During haemodynamic monitoring blood pressure was measured in addition (T_{P_card}, P_{sys_card}, P_{dia_card}, F_{card}). Derived blood pressure values were intradialytic mean arterial pressure (*e.g.* P_{mean1}), intradialytic pulse pressure (*e.g.* P_{pulse1}). Changes between pressures were calculated as the the difference between the first and the last intradialytic blood pressure value (P_{change_sys}, P_{change_dia}, F_{change}). Since – contrary to the predialytic blood pressure - the first intradialytic blood pressure value was measured under the same conditions (same device, same position on the dialysis chair) as the last intradialytic value, it was preferred to take the first intradialytic blood pressure as the baseline value. Further pressure changes were the absolute change between the mean arterial pressures before and after treatment named P_{change} and the relative change called I_{P_change}.

10.2.3.2.2 Mass and Volumes

Body mass (M_{treat_pre}, M_{treat_post}) was recorded for treatment purpose before and after every ultrafiltration treatment. It was measured by the standard balances of the dialysis unit, which were calibrated electronic column scales and certificated medical devices (*Medizinische Waagen und Messsysteme seca gmbh & co. kg.*, Hammer Steindamm 9-25, 22089 Hamburg, Germany and *RADMAG Magi Elektroniczne*, Bracka 28, 26-600 Radom, Poland). Patients remained dressed, but used to weighing procedure, they were aware that they had to carry the same clothes as for the last measuring procedure. Consequently, absolute values of M_{treat_pre} and M_{treat_post} are not correct, whereas changes in mass are reliable. The dry mass of a patient (M_{dry}) was that body mass, given by a physician, up to which fluid should be removed. The volume of the prescribed fluid removal corresponded to the variable V_{UF_prescr}. Because of unexpected events (side effects of the treatment, technical problems etc.), the prescribed volume targets might be not reached and the actually delivered volume change (V_{UF_deliv}) might be slightly different from the prescribed volume. Since the study subjects were chronic and stable HD patients, the difference between V_{UF_prescr} and V_{UF_deliv} was expected to be little. Ultrafiltration rate (Q_{UFV}) was defined as the volume removed per hour. Relative values were obtained by indexing absolute values to extracellular volume: relative prescribed ultrafiltration volume (I_{UFV_prescr}), relative delivered ultrafiltration volume (I_{UFV_deliv}) and relative ultrafiltration rate (I_{Q_UFV}).

10.2.3.2.3 Duration of the Treatment

We recorded the time of the start of ultrafiltration treatment (T_{start}), and the end of ultrafiltration treatment (T_{end}), the difference of the two time values was expressed as the duration of the ultrafiltration treatment ($T_{duration}$).

10.2.3.2.4 Ion Concentrations

Sodium concentration in the dialysate ($C_{natrium\_dialysate}$) was prescribed and known, the other ion concentrations were measured by *cobas b 221 system* (F. Hoffmann-La Roche AG, Grenzacherstrasse 124, CH-4070 Basel, Switzerland). Concentration of plasma sodium was measured at the beginning of dialysis ($C_{natrium\_serum}$). Blood bicarbonate concentration was evaluated before and after HD treatment (C_{HCO3_pre}, C_{HCO3_post}). Blood samples for these values were collected in EDTA vacuum tubes.

10.2.3.3 Haemodynamic Monitoring

Haemodynamic values were obtained by the *HD03* from *Transonic Systems Inc.* (34 Dutch Mill Road, Ithaca, NY 14850, United States of America). It is an indicator dilution method. The principle of dilution methods is that the higher the flow in the investigated system is, the more the indicator becomes diluted. Dilution is recorded over the time, yielding a curve in a concentration-time chart. The indicator used for the *HD03* is a 0.9 [%] saline solution and the detection method is ultrasound (23). The

velocity of sound in blood is a measure of hematocrit and total protein concentration (24) and can be used to trace the dilution of isotonic saline.

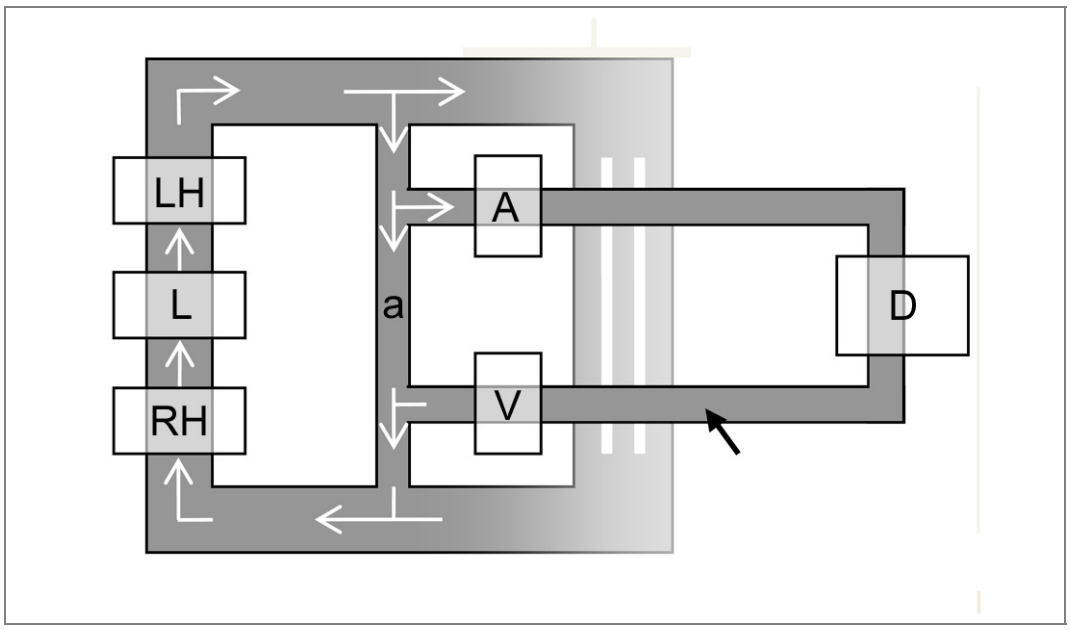

Fig 9 Haemodynamic monitoring using a saline dilution method
*Cardiopulmonary circuit with **RH** right heart, **L** lungs, **LH** left heart.*
*Extracorporal circuit with **A** arterial sensor, **V** venous sensor, **D** dialyser blood pump, injection site (black arrow).*
***a** access site*

The measurement was performed at the end of the HD treatment, defined as the second half of the treatment. Through the time of haemodynamic monitoring (T_{card}), the period to treatment end (T_{before_end}) could be deduced. The latter served as intern quality control.

10.2.3.3.1 Cardiac Output

A 10 [mL] calibration bolus of 0.9% saline solution with body temperature (33-38°C) was injected in the venous limb of extracorporal circulation upstream from the venous sensor as described by Kritviski et al (25). The venous sensor recorded the dilution signal over the time (calibration dilution curve). A second but larger saline bolus of 30 [mL] was injected, the bolus entered into the venous system, on its way to the heart it was mixed with the blood from the rest of the body, then the diluted bolus passed the right heart, the circulation of the lungs, the left heart, the great arteries. Before passing the body periphery, a part entered into the access site and in the arterial bloodline, where a sensor measured the dilution (cardiac output dilution curve). The higher the cardiac output (Q_{card}), the more the saline solution became diluted and consequently, the smaller the area under the cardiac output curve was in comparison to the area under the calibration curve.

Recirculation phenomena are major pitfalls of this method: Access recirculation is the inverse flow in the arteriovenous fistula and can be pre-existing or be induced, *e.g.* by the quick injection of a large bolus. If there is a recirculation, a part of the bolus will very quickly return by the access to the arterial line and the arterial sensor will record an additional dilution curve (access recirculation curve) before

the cardiac ouput curve. Access recirculation can be reduced by the decrease of the dialysis pump flow to the level of 250 to 300 [mL/min] (25).

The heart and the lungs are supplied with oxygen by their own circulation (e.g. the coronary arteries) and hence, blood from the thoracic aorta returns to the right atrium. This reverse blood flow is known as cardiopulmonary recirculation (CPR). That part of the bolus which passed by cardiopulmonary recirculation will arrive later at the sensor of the arterial bloodline as the bolus, resulting in a additional dilution curve (CPR curve). In order that the CPR curve and the cardiac output curve do not overlap, a quick injection lasting only several seconds is recommended.

10.2.3.3.2 Central Blood Volume

Central blood volume (V_{CBV}), also called needle-to-needle-volume, is equal to cardiac output multiplied by transit time. Transit time is equal to the time passed between the venous and the arterial curve from the cardiac output measure minus the time in the bloodlines. The corresponding indexed value was called central blood volume index (I_{CBVI}).

10.2.3.3.3 Derived Values of Cardiac Output

Cardiac index (I_{card}) was defined as cardiac output divided by body surface area. Another derived values was stroke volume (V_{SV}). Parameters called modified (Q_{card_mod}, I_{card_mod}) tried to take into account the influence of access flow on cardiac output. Their equations were derived from the relation between access flow and cardiac output empirically established by *Basile et al.* (26).

Physics defines resistance as the potential at a given flow. In blood circulation systems, potential corresponds to the pressure difference between arterial and venous system (here it was simplified as mean arterial pressure). The input for flow varies with the system: cardiac output, access flow,... Examples of resistance values are total peripheral resistance (R_{tot}) and total peripheral resistance index (I_{R_tot}).

Access blood flow bypasses the capillary bed and hence the systemic tissue compartments. That part of cardiac output that is available for the oxygenation of body tissues is called systemic cardiac output (I_{card_system}). It is definded as cardiac output minus access flow. Other systemic haemodynamic values are R_{system} and I_{R_system}.

10.2.3.3.4 Access Flow

The *Krivitski Method* (27) allows a quantification of the access flow (Q_A) if the extracorporeal blood flow (Q_B) is known. After the stop of the dialysis blood pump, the position of the bloodlines was reversed from normal: The venous outlet was placed upstream from the arterial inlet. 10 [mL] of 0.9% saline solution were injected in the venous bubble trap. The blood pump was restarted, the saline solution was mixed with the access flow at its entry into the arteriovenous fistula. Part of the resulting

total flow entered the arterial bloodline, where the dilution curve of the total flow ($Q_A + Q_B$) was measured.

Access resistance (R_{QA}) was the resistance of the arterio-venous fistula. The interest in measurement access flow is that values that are too low reveal future lacks of volume removal. Excessively high values – it is the ratio access flow to cardiac output (I_{QA/Q_card}) that is decisive here - may indicate a haemodynamic strain. Some time ago, it was proposed to define the ratio of access flow to cardiac output as cardiopulmonary recirculation (28) and values up to 50 [%] were found (29).

10.2.4 Dialysis Procedure

Dialysis conditions such as ultrafiltration rate and ultrafiltration volume were not deliberately changed for study purpose. Patients followed their normal thrice-weekly dialysis schedule. A treatment session took between 3:45 [h:min] and 5:00 [h:min].

10.2.4.1.1.1 Type of the Dialysis Membrane

The majority of dialysers in use came from the *Polyflux* product line from *Gambro AB* (Regeringsgatan 29, 10391 Stockholm, Sweden). High-flux mode is indicated by an *"H"* as the last digit of the product name (*Polyflux 170H*, *Polyflux 210H*). Low-flux dialysers used were *Polyflux 17L* and *Polyflux 21L*. Four patients had a *Xenium 210 G* dialyser from *Baxter International Inc.* (One Baxter Parkway, Deerfield, IL 60015-4633, United States of America). Product names were encoded to the variable "type of dialysis membrane" ($N_{membrane}$). In total, in ten patients low-flux models were used, in eighteen high-flux models.

10.2.4.1.1.2 Dialysis Machines

The haemodialysis machines from *Gambro AB* in use were *AK 200 S* and *AK 200 Ultra S*. Moreover, the dialysis unit was equipped with dialysis machines from *Fresenius Medical Care* (*4008 H*, *5008 H*). For the companies' addresses, please refer to previous chapters.

10.3 Data Analysis

10.3.1 Variables

The naming rules for the variables and a list of all variables used in the present study are attached in the appendix.

10.3.2 Statistical Software

The case report was done in *Excel 2002* from *Microsoft Corporation* (1 Microsoft Way, Redmond, WA 98052-8300, United States of America). In the same programme, derived parameters such as cardiac index were calculated. The data was later transferred to *SPSS 17* from *IBM Corporation* (1 New

Orchard Road, Armonk, New York 10504-1722, United States of America), which was used to perform statistical analysis.

10.3.3 Statistical Means

10.3.3.1 Correlations

In the case of ratio values, *Pearson* was used for examining correlations. For ordinal values, *Spearman* was applied. A probability $p<0.05$ was considered as significant to reject the null-hypothesis. The number of patients examined was twenty-eight, unless mentioned otherwise.

10.3.3.2 Comparison of Groups

Means of ratio values are displayed as arithmetic mean ± standard deviation for ratio values respectively as median ± interquartile range for ordinal values. Groups were examined by the *Kolmogorov-Smirnov* and *Shapiro-Wilk Tests*. A probability $p>0.05$ in the *Shapiro-Wilk Test* was considered as significant to assume normal distribution. Groups of nominal values were compared by χ^2*-Test*. Equal variances in the groups were assumed. Groups of normally distributed ratio values were compared by two-side *t-Test*. Ratio values without normal distribution and ordinal values were compared by *Wilcoxon Signed Ranks Test* (dependent samples) and *Mann-Whitney Test* (independent samples). For all tests, the probability for significant differences between groups was set at $p<0.05$.

11 RESULTS

11.1 Patient Characteristics

The baseline measurement was performed in all twenty-eight study participants (seventeen males and eleven females). The follow-up study included eight of the participants. The results presented in this chapter refer to the total study population and to the baseline measurement. Patient characteristics are shown in Tab 11-1. Six patients (21.4 [%]) were diabetics. Ten patients (35.7 [%]) had no antihypertensive medication, four patients (14.3 [%]) had an antihypertensive monotherapy and half of the study population took between two and four antihypertensives.

Tab 11-1 General patient characteristics

Body mass Index [kg/m²]	26.8	±6.0	(18.5 – 40.9)
Age [years]	51.3	±13.3	(18 – 73)
Predialytic mass [kg]	76.9	±19.4	(45.2 – 122.0)
Body height [m]	1.69	±0.09	(1.56 – 1.87)
Body surface area [m²]	1.87	±0.24	(1.42 – 2.38)
Treatment duration [h:min]	4:11	±0:24	(2:54 – 5 :00)

11.2 Indicators of Volume State

11.2.1 Bioimpedance and Anthropometry

Fluid volumes derived from bioimpedance are given in Tab 11-2. The total body water volume from the *Watson Equation* is attached in the last row of the table. Bioimpedance and *Watson Equation* had very similar results for total body water volume (r=0.891; p≤0.000).

Tab 11-2 Bioimpedance (B) and anthropometry (W) results

B: Extracellular volume [L]	17.9	±3.5	(11.7 – 26)
B: $I_{ECW/ICW}$ [ ]	0.97	±0.15	(0.73 – 1.30)
B: Predialytic volume overload [L]	2.1	±1.5	(-0.5 – 5.0)
B: Postdialytic volume overload [L]	0.1	±1.9	(-3.3 – 3.6)
B: Total body water [L]	36.8	±7.4	(26.1 – 54.2)

W: Total body water [L]	39.4	±8.4	(25.8 – 57.9)

11.2.2 *NT-pro BNP*

NT-pro BNP dropped during ultrafiltration treatment. Excluding subjects with NT-pro BNP values above the laboratory treshhold of 35000 [pg/mL], the mean relative change in NT-pro BNP was -20.8±30.9 [%]. There was no significant correlation between NT-pro BNP and blood pressure at the beginning or at the end of dialysis.

Tab 11-3 Comparison of NT-pro BNP levels
*^{pre} predialytic NT-pro BNP, ^{post} postdialyic NT-pro BNP, * significant difference, ˜ normal distribution, # other distribution*

	NT-pro BNP [pg/mL]			**NT-pro BNP** [pg/mL]		***p*-Value**
Predialytic	9332	±10068 #		Postdialytic	6995	±8242 #	≤0.016 *
Residual Urine	6830	±9428 # pre		No residual urine	11818	±10732 ˜ pre	≤0.105
Residual Urine	6013	±9429 # post		Residual Urine	7812	±7561 # post	≤0.280

11.2.3 Blood Pressure and Antihypertensives

Among the individuals of the study sample, blood pressure evolved highly differently during ultrafiltration treatment: The maximum increase observed in a patient was 60.3 [%], the maximum decrease was -26.8 [%] .Mean blood pressure change was -3.4±17.1 [%]. Pre- and postdialytic values are given in Tab 11-4. Predialytic arterial pressures were not significantly different from the pressures at treatment end.

Tab 11-4 Blood pressures at treatment beginning and end
P_{sys} = systolic bood pressure; P_{dia} = diastolic blood pressure, P_{mean} = mean arterial pressure, F = heart rate
** significant difference, ˜ normal distribution, # other distribution*

	Predialytic		**Postdialytic**		***p*-Value**
P_{sys} [mmHg]	134.8	±25.1 ˜	127.7	±25.8 ˜	≤0.103
P_{dia} [mmHg]	78.5	±16.3 ˜	75.9	±16.3 ˜	≤0.297
P_{mean} [mmHg]	97.3	±17.1 ˜	93.1	±18.2 ˜	≤0.170
F [bpm]	76.7	±13.7 #	75.1	±14.0 ˜	≤0.330

There was a positive but insignificant relationship between predialytic mean arterial pressure and the number of antihypertensive drugs taken (r=0.360; p≤0.060; *Spearman Test*). A comparison between

the eighteen patients with antihypertensives and the ten patients without medication is shown in Tab 11-5.

Tab 11-5 Antihypertensives patient group (AH) vs. No-Antihypertensives group (No AH)
** significant difference between the two patient groups, ˜ normal distribution, # other distribution*

	AH		No AH		*p*-Value
I_{BMI} [kg/m²] *	24.7	±4.9 #	30.7	±6.0 ˜	≤0.009 *
N_{age} [years] *	47.1	±13.6 ˜	59.0	±9.0 ˜	≤0.020 *
I_{VO_pre} [%]	13.1	±8.3 ˜	9.0	±7.7 ˜	≤0.216
P_{mean_pre} [mmHg]	106.0	±14.1 ˜	96.5	±17.5 ˜	≤0.129

11.2.4 Clinical Volume Score

The median of the clinical volume score was zero. Quartile ranges were at -2.75 respectively 0.75 (negative values indicate volume depletion, positive indicate volume overload). In twelve patients, volume state seemed to be normal (score at zero). In seven patients, the score was positive and in nine, it was negative.

11.2.5 Short Clinical Examination

Moist râles were detected in four patients. In twenty-one, they were not observed. Three patients were not auscultated. Bilateral œdema of the legs were found in six patients, whereas œdema were absent in twenty patients. Two patients were not examined in regard to œdema.

11.3 Correlations between Volume Indicators

Tab 11-6 Correlations between volume indicators
** significant correlation, [A] ratio between extracellular and intracellular volume, [B] mean arterial pressures before the treatment respectively at treatment end, [C] no correlation with other volume indicators, [D] Spearman*

		r-Value	*p*-Value
$I_{ECW/ICW}$ [A]	Relative predialytic volume overload	0.521	≤0.004 *
Predialytic NT-pro BNP	Relative predialytic volume overload	0.581	≤0.001 *
Predialytic NT-pro BNP	$I_{ECW/ICW}$ [A]	0.445	≤0.018 *
Blood pressure (predialytic) [B C]	Wizemann Score [C]	0.408	≤0.031 * [D]
Postdialytic NT-pro BNP	Relative postdialytic volume overload	0.470	≤0.012 *
Blood pressure (end) [B]	Relative postdialytic volume overload	0.436	≤0.020 *

The ratio between extracellular and intracellular volume correlated positively with the relative predialytic volume overload. Other volume indicators are provided by the plasma levels of NT-pro BNP. Strong correlations were observed between NT-pro BNP and volume indicators as determined by bioimpedance analysis (Tab 11-6 and Fig 10).

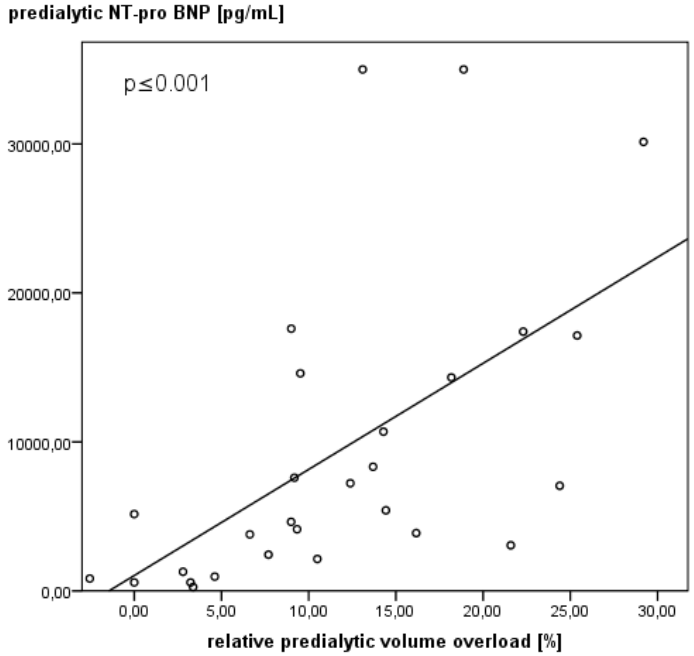

Fig 10 Relative predialytic volume overload and predialytic NT-pro BNP
A strong relationship between the two volume indicators was found (r=0.581; p≤0.001).

Please notice the upper limit for NT-pro BNP values at 35.000 [pg/mL] due to technical reasons and the effect of this threshold on computation of correlations coefficients, regression coefficients, and probabilities. For *Pearson* calculations, the two values that exceeded this upper limit were considered as if they were at 35.000 [pg/mL], the residuals from the regression line were erroneously small and the actual *p* was erroneously low.

The two postdialytic values, relative postdialytic volume overload and postdialytic NT-pro BNP, also correlated. In this case too, interpretation of NT-pro BNP may be disturbed by the upper limit of NT-pro BNP. Moreover, postdialytic values may be affected by predialytic values (Tab 11-7). Analysing the levels of postdialytic NT-pro BNP in two subgroups (high-flux versus low-flux), the relationship to postdialytic relative volume overload was found in the high-flux group (r=0.491; p≤0.039; n=18) but not in the low-flux group (r=0.447; p≤0.195; n=10).

Tab 11-7 Correlations between pre- and postdialytic values
** significant correlation*

	r-Value	*p*-Value
NT-pro BNP	0.890	≤0.000 *
Relative volume overload	0.867	≤0.000 *

Wizemann's clinical volume score correlated positively with postdialytic NT-pro BNP (r=0.391; p≤0.040, *Pearson*) but failed to correlate with more rigorous *Spearman* analysis. The clinical volume score can be considered as ordinal and as ratio variable, but *Spearman* (for ordinal variables) has to be preferred, because it is the more solid test. In *Spearman* analysis, the score showed a positive correlation with predialytic mean arterial pressure (Tab 11-6), but not with other volume indicators (pre- and postdialytic NT-pro BNP levels, pre- and postdialytic relative volume overload). Predialytic mean arterial pressure, however, was not related to any other volume indicator (ratio between extracellular and intracellular volume, predialytic volume overload, predialytic NT-pro BNP).

A comparison of clinical signs to relative volume overload obtained by bioimpedance is given in Tab 11-8. Symptoms of volume overload were compared to predialytic volume state, symptoms of volume depletion to postdialytic volume state.

Tab 11-8 Volume overload (I_{VO}) compared to clinical signs
** significant difference, ~ normal distribution, # other distribution, A relative volume overload after treatment, B relative volume overload before treatment*

	n	I_{VO} [%]			*n*	I_{VO} [%]		*p*-Value
Œdema	6	17.6	±8.6 ~ B	No œdema	20	9.3	±7.1 ~ B	≤0.025 *
Râles	4	17.8	±5.7 ~ B	No râles	21	10.3	±8.1 ~ B	≤0.096
Cramps	6	-7.6	±7.8 ~ A	No cramps	22	2.8	±11.4 ~ A	≤0.048 *
Hypotension	6	6.7	±10.0 ~ A	No Hypotension	22	-1.1	±11.5 ~ A	≤0.144
Fatigue	7	-0.4	±11.4 ~ A	No Fatigue	21	3.5	±12.3 ~ A	≤0.440

Mean arterial pressure, measured at treatment end (P_{mean8}), was significantly linked to relative postdialytic volume overload, whereas its correlation to postdialytic NT-pro BNP did not reach a significant level (Fig 11).

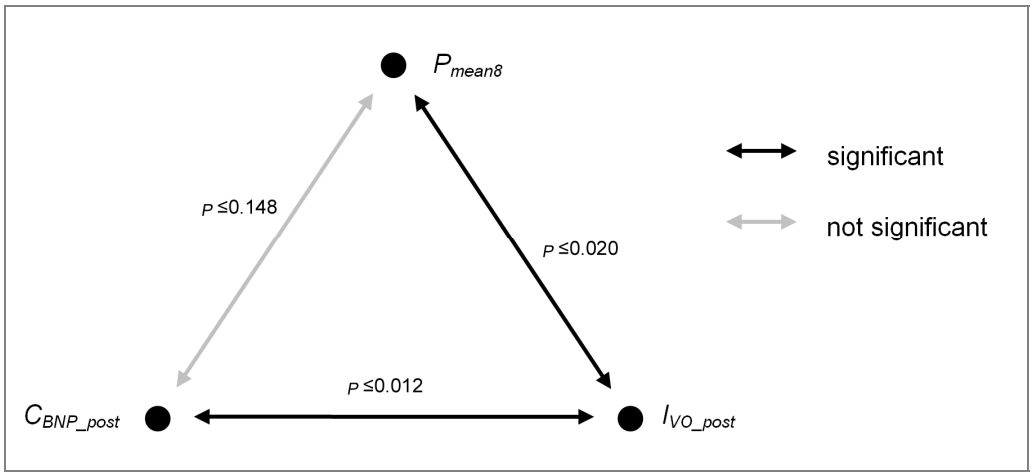

Fig 11 Correlations between postdialytic volume markers
Statistically significant relationships are depicted as black arrows, not significant relationhips as gray arrows.

Predialytic NT-pro BNP was negatively related to intracellular volume (r=-0.526; p≤0.004) and to total body water volume (r=-0.474; p≤0.011).

11.4 From Diagnosis to Treatment – Volume Overload versus Ultrafiltration Volumes

11.4.1 Change of Volume Indicators Related to Ultrafiltration Volume

The change between predialytic and postdialytic mean arterial pressure (P_{change}) was negatively related to postdialytic volume overload (r=-0.395; p≤0.038). This relationship became stronger if the variable for the absolute blood drop (P_{change}) was replaced by the variable for the relative blood drop (I_{P_change}). The blood pressure drop depended furthermore on the fraction of extracellular water volume that was removed by ultrafiltration (r=-0.511; p≤0.005).

Subjects with NT-pro BNP values above the treshhold of 35000 [pg/mL] were excluded from the evaluation of NT-pro BNP change. Relative change of NT-pro BNP (I_{BNP_change}) was not significantly correlated to relative ultrafiltration volume (r=-0.289; p≤0.153; n=26), nor were other BNP values (C_{BNP_change}, C_{BNP_post}). When relative change of NT-pro BNP was divided into two subgroups (high-flux versus low flux), the values of the low-flux subgroups correlated positively with relative ultrafiltration volume (r=0.730; p≤0.026; n=9). In the high-flux group, this relationship was absent (r=-0.148; p≤0.572; n=17).

11.4.2 Relation between Ultrafiltration Volume and Volume Indicators

Ultrafiltration volume was between 0.0 and 4.8 [L]. Mean ultrafiltration volume was 2.41±1.03 [L]. It was not significantly different from predialytic volume overload, which was 2.08±1.49 [L]. There was no significant positive correlation between ultrafiltration volume and predialytic volume overload. The relation between the two parameters even showed a weak negative trend (r=-0.145; p≤0.461) (Fig 12).

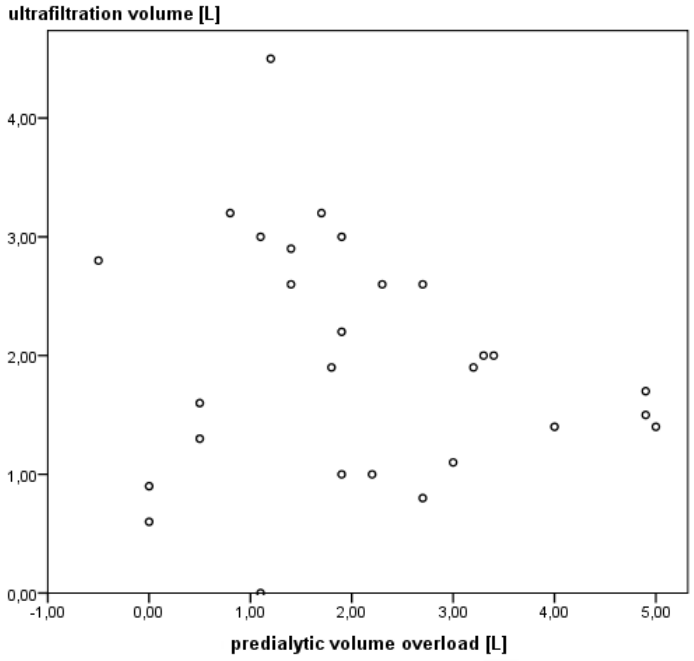

Fig 12 Prescribed ultrafiltration volume and predialytic volume overload
Surprisingly, ultrafiltration volume was not related to volume overload before treatment.

Relative ultrafiltration volume was not related to the ratio between extracellular and intracellular volume (r=-0.002; p≤0.992), nor to further volume indicators, like predialytic NT-pro BNP, predialytic mean arterial pressure or clinical volume score.

Correlation between postdialytic volume overload and delivered ultrafiltration volume was highly negative (r=-0.617; p≤0.000). Ultrafiltration volume corresponded to extracellular water volume (r=0.505; p≤0.006). Both correlated strongly with body surface area (A_{BSA}): r=0.886; p≤0.000 (comparing extracellular volume to A_{BSA}), respectively r=0.491; p≤0.008 (comparing ultrafiltration volume to A_{BSA}).

11.5 Reasons for the Discrepancies between Clinical and "Objective" Dry Mass

Various factors were investigated that might explain the discrepancies between volume overload, measured by bioimpedance, and ultrafiltration volume, assessed by physicians. However, patient age, cardiac index, serum albumin were not significantly related to relative postdialytic volume overload, as shown in Tab 11-9. Similarly, relative postdialytic volume overload was not significantly different in diabetics compared to non-diabetcs (p≤0.209, *t-Test*). Normal distribution was assumed (p≤0.454 in the diabetics group, p≤0.199 in the non-diabetics group, *Shapiro-Wilk Test*).

Tab 11-9 Relative postdialytic volume overload (I_{VO_post})
** significant correlation, [A] n=23*

		r-Value	*p*-Value
I_{VO_post}	Patient age	0.101	≤0.610
I_{VO_post}	Cardiac index [A]	-0.048	≤0.828
I_{VO_post}	Albumin	0.068	≤0.732

11.6 Cardiac Situation

11.6.1 Cardiac Performance and Fluid Status

Tab 11-10 Cardiac index (I_{card}) compared to volume indicators
** significant correlation, n=23*

		r-Value	*p*-Value
I_{card}	Relative predialytic volume overload	-0.175	≤0.424
I_{card}	Relative postdialytic volume overload	-0.048	≤0.828
I_{card}	Ratio between extracellular and intracellular volume	-0.493	≤0.017 *

Mean cardiac index was 2.81±0.59 [L/min/m²]. There was no correlation between cardiac index and pre- or postdialytic volume overload (Tab 11-10). Other cardiac parameters, like systematic cardiac index or modified cardiac index, did not correlate with volume overload either.

Cardiac index (I_{card}) and the ratio between extracellular and intracellular volume ($I_{ECW/ICW}$) correlated negatively. Similar correlations were found between other cardiac parameters and $I_{ECW/ICW}$. Both, I_{card} and $I_{ECW/ICW}$, depended strongly on age (chapter 11.6.2.2).

Cardiac index was not related to absolute blood pressure change (r=0.070; p≤0.751; n=23) nor to its relative change (r=0.114; p≤0.604; n=23).

11.6.2 Other Influences on Cardiac Performance

Apart from volume state, there were other factors that possibly influenced cardiac index:

11.6.2.1 Access Flow

Mean access flow was 1.02±0.47. The linear relationship between cardiac output and access flow (r=0.481; p≤0.020; n=23) was significant; however, statistical proof seemed weak. Consider that the

few outliers, whose access flow was 1.50 [L/min] or greater, had a strong impact on *Pearson* index compared to the multitude of other values.

The ratio between access flow and cardiac output was not related to the relative NT-pro BNP change (r=-0.018; p≤0.935; n=23). Only three ratios were above the limit of 0.30 [ ].

11.6.2.2 Other factors

Like other factors, cardiac index depended strongly on age (Tab 11-11). Cardiac index was not significantly different in female subjects compared to males (p≤0.968, *t-Test*). Normal distribution of cardiac index values was assumed (p≤0.653 for female subjects; p≤0.675 for male; *Shapiro-Wilk Test*).

Tab 11-11 Age-dependance of cardiac index and other values
** significant correlation, [A] n=23*

		r-Value	*p*-Value
Patient age	Cardiac index	-0.531	≤0.009 * [A]
Patient age	$I_{ECW/ICW}$	0.690	≤0.000 *
Patient age	I_{FAT}	0.577	≤0.001 *

11.6.3 Does Peripheral Resistance Depend on Volume Overload?

Tab 11-12 Total peripheral resistance index (I_{R_tot}) compared to volume indicators
** significant correlation, n=23*

		r-Value	*p*-Value
I_{R_tot}	Relative predialytic volume overload	0.444	≤0.034 *
I_{R_tot}	Ratio between extracellular and intracellular volume	0.562	≤0.005 *
I_{R_tot}	Postdialytic NT-pro BNP	0.518	≤0.011 *

Total peripheral resistance correlated with predialytic relative volume overload (r=0.660; p≤0.001; n=23). The derived value, total peripheral resistance index (I_{R_tot}), related positively to relative predialytic volume overload, too, but the correlation was weaker than the former (Tab 11-12 and Fig 13). I_{R_tot} also correlated with other indicators of volume overload (Tab 11-12).

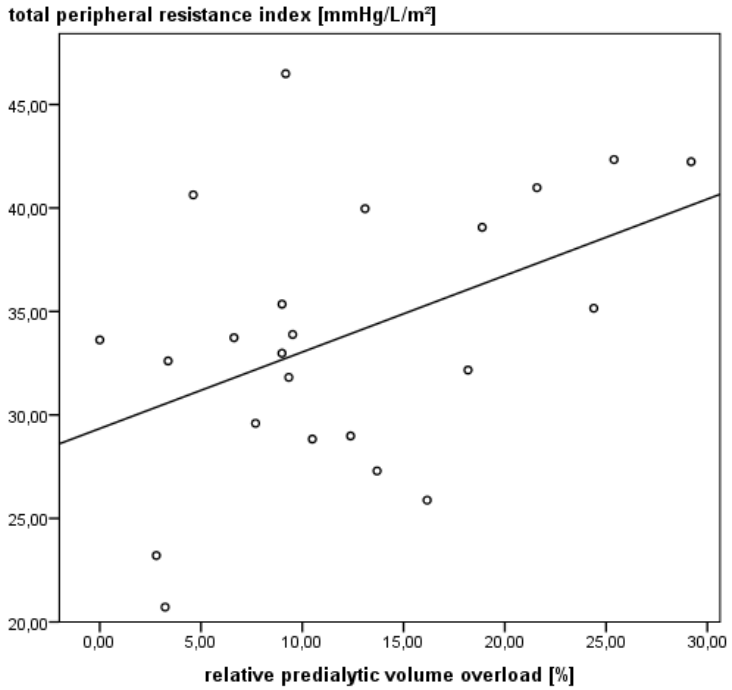

Fig 13 Total peripheral resistance index and predialytic relative volume overload
There was a positive correlation between the two parameters (r=0.444; p≤0.034; n=23).

Please note in [Fig 13] that there were two patients who may be regarded as outliers. They had, in comparison to the other patients, very low I_{R_tot} values (between 20 and 25 [mmHg/L/m²]) and their relative volume overload was low, too. Since *Pearson* is strongly influenced by outliers, the values of these two patients maybe affected *Pearson's* calculation by simulating a positive correlation.

Total peripheral resistance index did not correlate with relative ultrafiltration rate (r=0.075; p≤0.733; n=23). It did not depend on age either.

11.7 Does Body Composition Confound the Calculation of Volume Overload?

11.7.1 Evaluation of Tissues

Mean adipose tissue mass was found at 36.9±20.2 [kg]. Mean lean tissue mass was 36.4±10.9 [kg]. Body mass index and relative fat mass correlated highly positively (r=0.745; p≤0.000). Positive correlations were similarly observed between anthropometric data suggesting obesity (mid upper arm circumference, body mass, waist-to-hip ratio) and adiposity parameters calculated by bioimpedance spectroscopy (fat tissue mass, adipose tissue mass, fat tissue index).

11.7.2 Influence of Body Composition on Volume Overload

A negative correlation between body mass index and relative predialytic volume overload was observed (r=-0.424; p≤0.024). Volume overload correlated negatively with other obesity parameters too.

11.8 Follow-up Study

Eight patients entered the follow-up study. The period between the baseline and the follow-up measurement was from fourteen to twenty-eight days. Body mass remained stable between the two dialysis study days: mean mass change was 0.3±0.9 [kg]. The maximum mass gain was 1.6 [kg], the maximum loss was 0.8 [kg]. A comparison between the changes of body mass and of volume indicators is given in Tab 11-13.

Tab 11-13 Changes in predialytic body mass (∆ M_{pre})
** significant correlation*

		r-Value	*p*-Value
∆ M_{pre}	Total body water	0.832	≤0.010 *
∆ M_{pre}	Predialytic volume overload	0.714	≤0.047 *
∆ M_{pre}	Extracellular volume	0.914	≤0.002 *

12 DISCUSSION

The high cardiovascular mortality in chronic kidney disease population may be a consequence of the disturbed volume state (1,2,30). In theoretical models, the relationship between volume state and cardiovascular system has been described (14), but there is a lack of studys that measure parameters of both systems at the same time. The present study investigated various indicators of volume state as well as cardiac output in chronic haemodialysis patients.

12.1 Patient Characteristics

The study participants were more or less representative of chronic haemodialysis patients. Mean age was found to be smaller than in epidemiological surveys of renal replacement therapy but was higher than in studies with comparable design (31,32). The range in body mass index and in age was high in the present study sample, so that their influence could be taken into account as well. Exclusion was only imposed by one of the measurement methods. Possibly enough, selection bias was induced by these exclusion criteria, though, because these criteria are more frequently present in subjects with high comorbidity.

12.2 Indicators of Volume State

Different indicators of volume overload have been the issue of recent research projects. None of them is entirely specific for volume state. Dilution methods are commonly accepted as the reference, but they are too complex to be implemented in clinical practice. Dilution methods measure the volumes of extracellular and intracellular compartment, but they do not replace the need for a model to interpret the measurement data.

Although promising, bioimpedance spectroscopy has rarely been used in clinical practice. The impedance data was expressed as vector (33-35), which was difficult to understand for physicians. Different models have been developed to transform the measurement data into information which is easier to interpret. A possibility is to simply relate extracellular volume either to intracellular or to total body water volume (31,36). These three volumes are obtained by bioimpedance spectroscopy. A recent model, which permits the quantification of volume overload, has been proposed by *Chamney et al.* (19). The *Chamney Model* was the basis of the device used in the present study. As volume overload could not be objectively quantified up to the recent past, literature is poor in reference data. In a patient sample examined by *Wizemann et al.* (7), mean volume overload was 1.4±1.6 [L] before and -0.7±1.6 [L] after treatment, respectively, and smaller compared to the present study (2.1±1.5 [L] before and 0.1±1.9 [L] after treatment).

The value of NT-pro BNP for the assessment of volume overload in hemodialysis patients has been questioned over the last years (37-42). Important to note, NT-pro BNP plasma levels are linked to various other factors as left ventricular myocardial mass, residual urine volume, inflammation and

dialysis procedure (43). In our patients sample, however, no significant differences were found between patients with residual renal function and those without. NT-pro BNP was not connected to blood pressure as a surrogate for left ventricular strain and thus for left ventricular mass. The permeability of the dialysis membrane, however, had a strong impact on the NT-pro BNP change. A NT-pro BNP decrease was observed during all treatment sessions with high-flux membrane, whereas NT-pro BNP increased or remained stable if low-flux membranes were applied. Since the pores of high-flux membranes tend to be larger than those of low-flux membranes, mid-molecular-mass molecules as NT-pro BNP[a] are usually better cleared through high-flux procedure (44). Without generation or clearance of a plasma component, the change in plasma concentration is inversely proportional to the ultrafiltration induced changes in plasma volume. Thus, it was probably a concentration effect that led to an intradialytic NT-pro BNP increase in the low-flux group. Because of the large discrepancy between the high-flux and the low-flux groups, postdialytic NT-pro BNP plasma levels and NT-pro BNP change should be analysed separately in both groups.

In the whole study population, NT-pro BNP plasma levels were significantly higher at the beginning than at the end of the treatment. Studies disagree on the half-life value for NT-pro BNP. In literature, values between 60 and 120 [min] (45) have been reported. Hence, it cannot be excluded that the postdialytic levels were also affected by baseline levels measured before dialysis. If a half-life value of 90 [min] is assumed, between 9.9 and 17.7 [%] of the original predialytic level would be available at treatment end, depending on the duration of treatment, which was between 5:00 and 3:45 [h:min]. The NT-pro BNP release is sensitive to the overload in blood volume, as the NT-pro BNP receptors are located within the cardiovascular system. Blood volume overload correlates in equilibrium to the expansion of the whole extracellular compartment, in short, to volume overload. In disequilibrium, as induced by ultrafiltration treatment, this relationship between extracellular and blood volume is not present any more. Contrary to predialytic NT-pro BNP levels, postdialytic levels reflect blood volume but not extracellular volume and they are influenced by additional factors such as clearance differences depending on dialysis membrane permeability.

[a]The molecular mass of NTpro BNP is 8.5 [kDa].

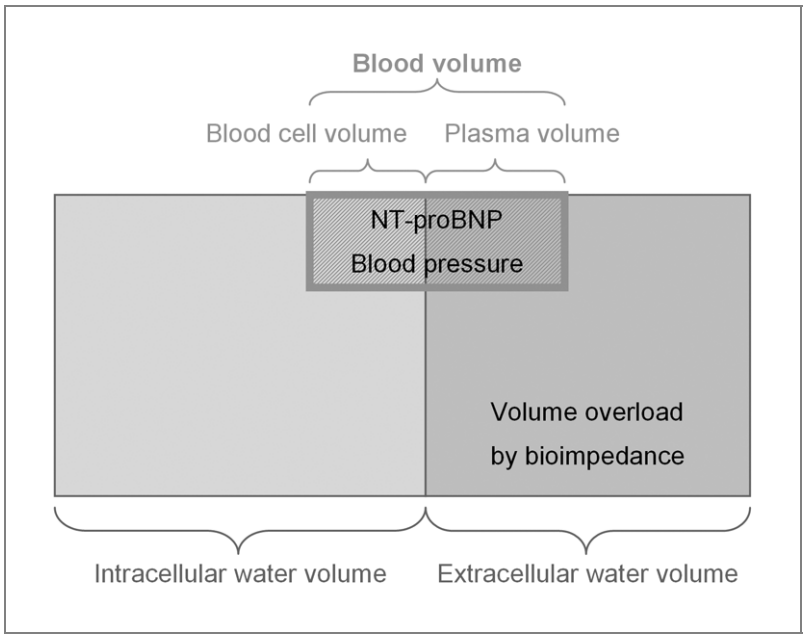

Fig 14 Body water compartments and volume indicators
Volume indicators (black font colour) reflect only certain compartments (grey font colour). Only in equilibrium, the indicators may represent also other compartments – modified from Mees (1).

High interindividual differences were observed in the evolution of blood pressure during ultrafiltration treatment. The values after treatment consequently were not significantly different from the values before treatment. Patients taking antihypertensive medication had high predialytic blood pressure values, but these pressures were not significantly different from those in patients taking no drugs. Without doubt, medication as a single strategy to control blood pressure is not sufficient in haemodialysis patients. The cornerstone in blood pressure control is strict volume therapy. In the present study, relative predialytic volume overload was not significantly different between patients with and those without antihypertensives. For the relationship between blood pressure and volume overload, please refer to chapter 12.3. Considering the pathomechanisms of arterial hypertension, it was surprising that the patients with antihypertensives were younger and less obese than those without medication.

Contrary to other volume indicators, *Wizemann's* clinical volume score does not reflect volume state at a certain point of time time such as at the beginning of the treatment, but it assesses volume overload throughout the whole cycle of dialytic volume removal and interdialytic volume gain. These different time scales prevent a comparison with other volume indicators. The score was zero in nearly half of the study participants for the whole cycle, indicating normal volume state. Values of volume depletion and of volume overload were more or less equally present in the study population.

Bilateral leg œdema and moist râles were absent in the majority of patients. This finding cannot be brought forward as an argument for the accuracy of volume therapy, since these clinical symptoms are unspecific and are present only in severe cases of volume disorders.

The values of total body water volume were supported by the results of *Watson* equation. Anthropometry, however, is of little help to charaterize the volume state, because this method assumes normal volume state to calculate the respective water volumes. Consequently, anthropometric data may be suited as a validation tool for fluid volumes but not for the detection of volume overload as obtained by the *Chamney Model*.

12.3 Correlations between Volume Indicators

Since volume indicators, even those called “objective”, may not reflect the true volume state, the comparison of the different methods was the first important step in the present study. Crucial for all comparisons is that the measured indicators should reflect volume overload at the same point of time or during the same period. Moreover, comparisons require either two absolute volumes or two relative volumes.

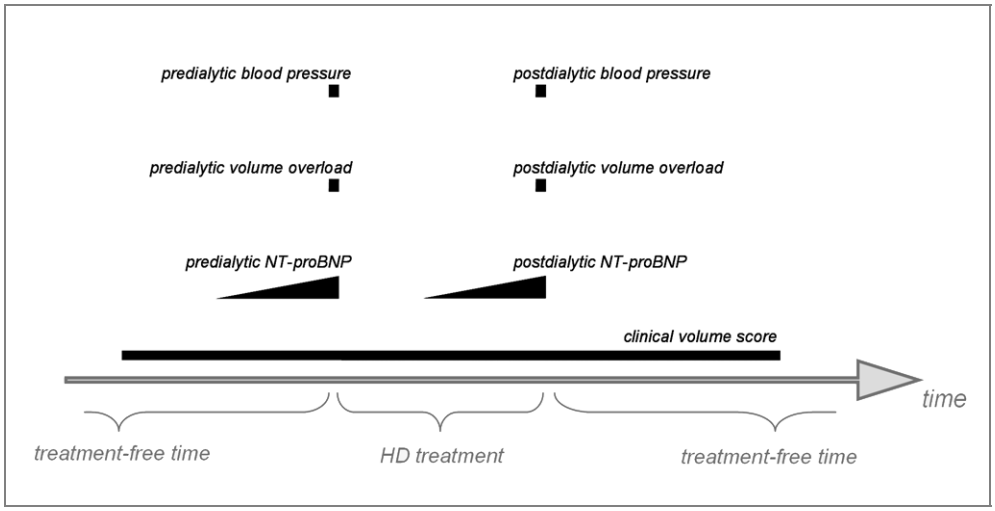

Fig 15 Time scales of different volume indicators
The black areas represent the time dimension of the respective indicator.

Indicators of predialytic volume state were numerous and easy to compare, since body fluids are in equilibrium at the beginning of the treatment.

Bioimpedance spectroscopy provided two volume indicators, the relative volume overload of the *Chamney Model* and the extracellular-to-intracellular-volume ratio. They were strongly related to each other (r=0.521). Considering that both are based on the same measurement method, relationship could be expected to be even stronger. This finding suggests that the relative volume overload of the *Chamney Model* provides additional information in comparison to the earlier idea of extracellular-to-intracellular-volume ratio. Whether this additional information reflects the volume state more correctly, has to be investigated in further studies.

Predialytic volume state as assessed by bioimpedance spectroscopy was confirmed by predialytic NT-pro BNP plasma levels. The relationship between NT-pro BNP and bioimpedance was so strong that it

cannot be disputed, even if the correlation was likely to be blunted by the upper threshold of NT-pro BNP measurements.

Chamney's relative volume overload was significantly larger in patients with bilateral leg œdema. It was not larger in patients with pulmonary moist râles: firstly, so-called whole-body bioimpedance is not suited to assess the volume state in the trunk, because the trunk contributes only little to overall resistance (46-48). Secondly, the accuracy of the lung auscultation can be questioned, because the assessment of moist râles is difficult and dependent on the clinical experience of the investigator.

There is a consensus in the scientific community that volume overload is one of the decisive causes of arterial hypertension in haemodialysis patients (1). However, predialytic blood pressure was not statistically linked to volume state as assessed by bioimpedance and NT-pro BNP. This lack of relationship is likely to be due to the diversity of factors that influence blood pressure. Postdialytic blood pressure, however, was related to relative postdialytic volume overload. This statistical relationship was rather unexpected, considering the physiological mechanism of volume shifts during dialysis: blood volume at the end of ultrafiltration and consequently blood pressure are no longer determined by the size of the extracellular compartment but by hypovolaemia caused by inadequate vascular refilling. For a similar reason, the interpretation of the relation was difficult, which was observed between the postdialytic values of relative volume overload and of NT-pro BNP. The first variable is a function of the size of the extracellular compartment, the second, though, reflects blood volume. There are two hypotheses to explain the relationship between the extracellular compartment and the blood volume indicators (NT-pro BNP, blood pressure) at the end of the treatment:

1) NT-pro BNP and blood pressure values in non-steady-state were unreliable blood volume markers.

2) Steady-state had already been reached at the end of the treatment. Thus, postdialytic blood volume was reflected by postdialytic extracellular volume.

The first hypothesis seems more likely: The limited value of NT-pro BNP as postdialytic blood volume indicator has already been shown in the chapter 12.2. Moreover, in a separate analysis, the relation between NT-pro BNP and the extracellular compartment was only confirmed in the high-flux group but not in the low-flux group.

The negative relationships found between NT-pro BNP plasma levels and the volumes of intracellular and total body water compartment cannot be interpreted, because a relative measure (NT-pro BNP = concentration) is compared to absolutes measures (water compartments = volume).

Comparison of the *Wizemann* Score was difficult, since the score had another time scale than the other volume indicators. Hence, even the sole relationship found, which was with predialytic mean arterial pressure, has to be questioned. However, the predialytic values of volume indicators are

sensitive to the duration of the interdialytic interval as well as to the accumulation or generation rate. This is comparable to the levels of urea and other solutes measured predialysis.

Adverse effects (cramps, hypotension, fatigue) of dialysis treatment were compared to volume depletion at the end of the treatment. Since volume depletion was more pronounced in patients with cramps, this adverse effect was presumably due to the ambitious volume targets in these patients. However, it could not be shown that the two other adverse effects (hypotension and fatigue) depend on volume state.

To sum up, it has been possible to show relationships between predialytic volume indicators. In some cases, correlation between volume indicators was absent, which may be due to non-specificity and to different time or volume dimension of the compared values. As significant positive correlations prevailed between them, the predialytic volume indicators measured the same physiological process, which in all likelihood was tantamount to volume overload. Some of the postdialytic volume indicators were also related to each other, but their accuracy could not be confirmed, because they were affected by additional factors as compared with predialytic variables, and they represented other volumes.

12.4 From Diagnosis to Treatment – Volume Overload versus Ultrafiltration Volumes

12.4.1 Change of Volume Indicators Related to Ultrafiltration Volume

The two volume indicators, which were measured before and after treatment, were blood pressure and NT-pro BNP. It was expected that the change of the two variables was related to the volume change induced by ultrafiltration. In spite of a positive trend between the two variables, NT-pro BNP changes were not significantly related to ultrafiltration treatment. In separate analysis for the low-flux group, NT-pro BNP even increased with the fraction of extracellular compartment removed by ultrafiltration. This may be due to the low clearance of NT-pro BNP by low-flux membranes and to a concentration effect, caused by the reduction in plasma volume. The high-flux group did not significantly reflect volume removal either, but NT-pro BNP tended to drop with volume removal. At this stage, it is not possible to separate the two main influences on postdialytic NT-pro BNP, which are the mentioned concentration effect and volume state, but one could account for haemoconcentration by referring the changes in NT-pro BNP to the changes in blood volume or in plasma volume. Changes in blood/plasma volume can be estimated by changes in haematocrit/plasma protein concentration. Consequently, the value of postdialytic NT-pro BNP for the description of volume state is limited. As the concentration effect is larger in the low-flux group, interpretation of postdialytic NT-pro BNP in this group is even more restricted.

A volume-dependent NT-pro BNP change could have been assumed from the fact that predialytic and postdialytic NT-pro BNP plasma levels were linked to the respective volume overload (chapter 12.3). Possibly, the postdialytic relationship only mirrored the strong predialytic correlation.

As expected, mean arterial pressure fell more sharply if the relative ultrafiltration volume that was removed was large. Furthermore, blood pressure drop depended on the volume state. The more pronounced volume depletion was at dialysis end, the less volume could shift from the interstitial to the intracapillary compartment, and the more blood pressure fell.

To conclude, the blood pressure evolution reflects the volume change by ultrafiltration. NT-pro BNP, however, which increased in the low-flux group and decreased in the high-flux group, fails to reflect the volume change.

12.4.2 Relation between Ultrafiltration Volume and Volume Indicators

The target of ultrafiltration treatment is the removal of volume overload. Thus, it was expected that ultrafiltration volume would correspond to predialytic volume overload. Surprisingly, the relationship of the two variables showed a weak negative trend. In order words, there was a large discrepancy between clinical dry mass, which determines ultrafiltration volume, and the volume overload derived from bioimpedance measurement.

12.5 Reasons for the Discrepancies between Clinical and "Objective" Dry Mass

Explanations for the discrepancies between volume overload and ultrafiltration volume can be summarized by three hypotheses:

1) Physicians poorly evaluated ultrafiltration volume in the study patients.

2) The *Chamney Model* and its quantification of volume overload are inaccurate.

3) It was not possible in some patients to remove the whole volume overload because of comorbidity or of side effects of the treatment.

In the following chapters, these hypotheses will be discussed in detail.

12.5.1.1 Assessment of Dry Mass

The estimation of dry mass is difficult, because the symptoms of volume state are unspecific and are present only in severe cases of volume disorders. Even a consensus on the definition of dry mass does not exist, as shown in the introduction. Hence, it would not be surprising to find dry mass to be poorly evaluated in clinical practice. On the other hand, it can be assumed that the clinical assessment of dry mass was not worse in the present study sample than in the average haemodialysis patient. The study was conducted at a university hospital with large personal and technological resources: the physician staff is numerous and is confronted in its research projects with the need of strict volume control. Furthermore, NT-pro BNP was routinely measured every month.

12.5.1.2 Accuracy of the *Chamney Model*

The bioimpedance devices that have entered the market in the last two decades provided largely unprocessed information to be used for empirically derived equations using data from a reference population. These equations fail for subjects with other characteristics than those of the reference population. An abundance of input variables is used to compensate the resulting errors.

Devices with an underlying physiological model such that developed by *Chamney et al.* are to be preferred, because they are applicable to different populations. The *Chamney Model* is convincing because of its simplicity, its adherence to physiological principles and the small number of input variables. For a more detailed description of the model, please refer to chapter 10.2.2.5. In the present study, relationships with other volume indicators were found (chapter 12.3). Moreover, mass change was sufficiently reflected by the results of this model (chapter 12.8). This suggests that the *Chamney Model* is able to assess volume state not only at a point of time but also its change over the time.

A cornerstone of the *Chamney Model* is the assumption of constant water volume fractions in healthy tissues. For the quantification of these fractions, healthy subjects were examined. The following items of the *Chamney Model* may be criticised. The term “healthy” was not exactly defined (19). Furthermore, the sample size of 104 participants was small. Calculation of volume overload in subjects at the extremes of body mass index may be not accurate, as shown in chapter 12.7.2. In the *Chamney Model*, water volume fractions are considered as stable in the adult age group, but this is not certain, as they change significantly during childhood (49). It cannot be excluded that water volume fractions change with age in adults, too. Like other bioimpedance models, the *Chamney Model* assumes a fixed ratio of bone tissue to total protein mass. Such simplifications are necessary to develop a model but may lead to errors when the characteristics of the measured patient differ from the average patient. Since there is no consensus on the definition of volume overload and reference method for its quantification is missing, a validation of the *Chamney Model* is difficult. The model has been implemented only recently as *Body Composition Monitor* (*BCM*) in clinical practice so that it may be too early to judge the method, even if first promising data of *BCM* guided therapy have been published (50).

The accuracy of the *Chamney Model* depends on the accuracy of its input variables of its input variables such as body mass, intracellular, and extracellular volumes. Errors due to body mass are small, provided that the weighing procedure is carried out carefully. Intracellular and extracellular volumes are calculated from the bioimpedance data via the *Cole Model* and *Hanai Theory*. The *Cole Model* is rather descriptive than explanatory, but it has proved satisfactory, even in different populations. As stated by *Matthie*, “...many errors occur from the measurement itself rather than from the calculation by a model” (10). Challenges for research in this field are (10):

1) Skin and core temperature: a 1 [°C] change leads to a 2 [%] change of the resistivity.

2) Skin impedance: is smaller in moist skin than in dry skin.

3) Current density: is simplified to be equally distributed in all current paths in the body.

4) Anisotropy of the cells: impedance was found to be stronger *in vitro*, when the measurement was transverse, instead of parallel to the muscle cell axis.

5) Body geometry: in wrist-to-ankle methods, wrongly called whole-body measurements, the trunk contributes little to the overall resistance. Consequently, the composition of the trunk is estimated by the composition of the limbs, rather than measured. Moreover, consistent ratios between circumference and the length of a segment are assumed, and segments are considered as a cylinder, which is particularly wrong for the trunk of obese patients. This error is of modest effect, because of the low trunk resistance, *cf.* above.

6) Ion concentration: is assumed to be constant.

7) Orthostatic fluid shifts: fluid is equally distributed in the body only after several minutes of supine position - a time requirement, which will presumably be disobeyed in clinical practice.

12.5.1.3 Comorbidity and Side Effects

Comorbidity and side effects tend to obstruct volume control in the affected subjects. Among the factors to be considered, 1) age reflecting general comorbidity, 2) plasma albumin representing malnutrition, 3) diabetes, which is accompanied by episodes of intradialytic hypotension through a default of vessel adaptation, and 4) cardiac index as a surrogate for the cardiac situation. An impaired heart characterised by low cardiac index values, “needs” some volume overload to maintain appropriate diastolic filling, cardiac output, and blood pressure. Another marker of cardiac impairment is NT-pro BNP, widely used in clinical practice (51) and assessed in the present study. In dialysis patients such as in the present study, however, cardiac evaluation by NT-pro BNP is not reasonable, because NT-pro BNP levels are much more affected by volume state and residual renal function.

In our study population there was, as said before, a large discrepancy between ultrafiltration volume and other indicators of volume expansion. Postdialytic volume overload, however, was not linked to any of the comorbidity factors described in the paragraph above (age, plasma albumin, diabetes, cardiac index). Thus, the comorbidity factors could not explain the discrepancy between clinical and “objective” dry mass. Comorbidity as a cause for the observed discrepancy cannot be totally excluded, since the comorbidity factors, especially cardiac index, were only partly representative of the respective pathology. An argument against the hypothesis of comorbidity as the decisive cause for the discrepancy lies in the small comorbidity frequency in the examined patient sample: low cardiac index, defined as cardiac index ≤2 [L/m²/min], was measured in only three out of twenty-three patients. The albumin values were in a close range (41.8±2.9 [g/L]) and even the smallest values (36 [g/L]) did not indicate severe malnutrition.

Comorbidity but also side effects, *e.g.* cramps, had possibly led to an adaptation of dry mass. However, the side effects before the last adaptation were not assessed, only the side effects after the last adaptation, which were not the cause of the adaptation but its consequence.

The third factor that possibly constrains volume therapy is poor patient compliance, but the term compliance is difficult to quantify.

12.6 Cardiac Situation

12.6.1 Cardiac Performance and Fluid Status

12.6.1.1 Ultrafiltration Induces Changes in Fluid Status

The fast blood volume removal by ultrafiltration leads to a temporary disequilibrium of the body fluids. In the beginning, blood volume decreases excessively, because blood volume is removed more quickly than volume moves from the interstitial to the blood compartment. The mentioned volume shift, called plasma refill, is highly dependent on extracellular volume expansion, in other words, on predialytic volume overload. In patients with high predialytic volume overload, plasma refill takes place quickly, so that blood volume drop caused by ultrafiltration is compensated by plasma refill by the end of the dialysis treatment. In patients with little volume overload or even volume depletion before the treatment, plasma refill rate is low and blood volume may remain decreased beyond the end of the dialysis treatment. The difference between the plasma refill rates in these two patient groups is high. That is why dialysis treatment – similar volume removals assumed - amplifies the gap in blood volume between the two patient groups (high *vs.* low predialytic volume overload). Differences in blood volume consequently are more pronounced at the end of a treatment. However, the blood volume change has a wide interindividual range and can be obscured by compensatory mechanisms such as the down-regulation of the *splanchnicus* perfusion.

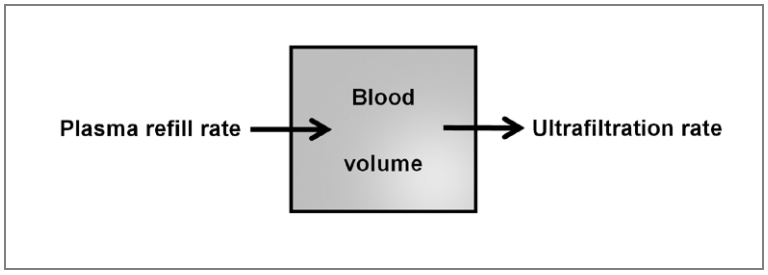

Fig 16 Blood volume change during dialysis
Blood volume change depends on ultrafiltration volume and the size of plasma refill.

Haemodynamic measurements were performed towards the end of a dialysis treatment session, when differences in blood volume become more visible. On the other hand, bioimpedance analysis done during dialysis or during the immediate post-dialysis period leads to spurious volume estimates because fluid volume distribution is perturbed by volume shifts between different compartments. For

this reason, bioimpedance measurement was performed before the treatment. Volume overload after treatment session is easily calculated if ultrafiltration volume is known.

Postdialytic volume overload, however, does not adequately reflect blood volume, the value relevant to haemodynamics, since fluid repartition is in disequilibrium at the end of the treatment. Therefore, the study design does not permit to quantify postdialytic blood volume. Acute changes of blood volume as induced by ultrafiltration treatment can be estimated by continuous monitoring of haematocrit. Under the assumption that the volume of the blood cells remains unchanged during ultrafiltration, a haematocrit rise is equal to a decrease of the plasma volume. It is not possible, however, to deduce the absolute value of blood volume nor its absolute change by haematocrit monitoring. Devices such as the *CritLine* would provide continuous haematocrit monitoring, but they were not integrated in the present study design.

NT-pro BNP plasma levels reflect blood volume to a certain degree, but as discussed, their value at dialysis end is limited for the evaluation of volume state. Moreover, a possible relationship between NT-pro BNP and cardiac index may be due, not to volume state but simply to the effect of the cardiac function on both values.

To sum up, differences in the haemodynamic situation due to fluid status are enhanced at the end of a treatment session, but the quantification of absolute blood volume was not possible at this time. Consequently, the current study cannot reveal the relationship between cardiac parameters and volume overload.

12.6.1.2 Low Cardiac Output through Volume Depletion?

It has been speculated that a very low cardiac index at the end of dialysis sessions could be indicative of excessive volume depletion (52,53). It was also reported that an adjustment of dry mass led to an improvement of the cardiac index in this patient group. Inappropriately low dry mass respectively volume depletion leads to diminished cardiac preload and in consequence to diminished afterload. However, only a part of low-cardiac-output syndromes can be blamed on volume depletion. In other patients, it is the myocardial dysfunction due to, *e.g.*, alterations of coronary arteries which leads to cardiac impairment and low cardiac index. Volume overload is essential for the heart of these patients to maintain a sufficient blood circulation. In other words, the low-cardiac-output group has to be separated into two subgroups with contrasting volume state. If examined, the whole low-cardiac-output group will probably not show a different mean volume overload compared to other patients, but the variability of the volume overload values will be higher.

12.6.1.3 Comparison of Cardiac Index to Volume Indicators

Unfortunately, the study was not appropriately designed to compare the cardiac index to the volume overload of the *Chamney Model*, as said before. Hence, it was not possible to interpret the absent correlations between cardiac index and volume overload and between their respective derived values.

The highly negative relationship between cardiac parameters and the extracellular-to-intracellular-volume ratio ($I_{ECW/ICW}$) is presumably not due to volume state but to a confounder, namely to body tissue composition. $I_{ECW/ICW}$ is greater in adipose tissue, thus high in older and obese subjects, whose cardiac index is small because of cardiac impairment or reduced oxygen need in the body periphery. This chain of ideas was supported by the data found in the present patient sample.

Since interpretation of postdialytic NT-pro BNP was difficult, comparison with the cardiac index was not possible. The blood pressure change may have reflected the change in blood volume. However, relationships between cardiac index and absolute, respectively relative blood pressure change were absent.

12.6.2 Other Influences on Cardiac Performance

Volume state is one among various factors with an effect on cardiac output. The most important factor is body size which is accounted for by indexing cardiac output to body surface area to obtain the cardiac index. Other factors have been described for the general and dialysis populations:

12.6.2.1 Age

In this study cardiac index strongly decreased with age. At higher age and with reduced lean body mass, organs need less oxygen and therefore, cardiac output diminishes. Furthermore, cardiac impairment inducing a decreased cardiac output is primarily a disease of higher age. Effects of age on the cardiac index were highly present in the study population, since their age range was large.

12.6.2.2 Cardiac Impairment

It is difficult to quantify cardiac impairment. Firstly, cardiac impairment is a clinical term without an exact definition. Secondly, its measurement is difficult and invasive, such as by cardiac catheterisation or requires a skilled examination, as with cardiac ultrasound (measurement of ejection fraction, myocardial dimensions).

12.6.2.3 Access Flow

As expected, there was a positive correlation between cardiac output and access flow. In a recent study, a non-linear relationship between the two variables was found (26). Explanation is given by physiological principles: on the one hand, access flow depends on mean arterial pressure, which is proportional to cardiac output (Q_{card}). On the other hand, access flow reduces total peripheral resistance, and the cardiac output has to increase to maintain the same arterial blood pressure. An access flow equal to 30 [%] of cardiac output or higher, is considered to be a risk factor of high-output cardiac failure (54). The haemodynamic strain may be reflected by NT-pro BNP plasma levels. In the present sample, no correlation between NT-pro BNP and the ratio between access flow and cardiac

output was found. The conclusion is limited, though, since only three participants exceeded this critical level of 30 [%].

To sum up, cardiac output drives access flow and *vice versa*. Since variable A affects variable B and variable B affects variable A (active and passive action), both variables are independent and dependent variables at the same time.

12.6.3 Does Peripheral Resistance Depend on Volume Overload?

The interpretation of resistance values has to be divided into chronic and acute reasons. Volume overload is only one of a multitude of factors that influence peripheral resistance. Examples of the role of volume overload: firstly, chronic volume overload, via arterial hypertension, leads to alterations and stiffness of the vessel wall. Secondly, according to an autoregulation concept proposed by *Hall et al.*, hypercirculation due to volume overload induces vasoconstriction in order to protect the tissues against this hypercirculatory state (1). Quick fluid removal leads to vasoconstriction in order to attenuate blood pressure drop and to maintain peripheral circulation.

Cardiac parameters could not be compared to the measured volume indicators, as said above. Of course, this applied for resistance values as well. Thus, the relationship found between the total peripheral resistance index (I_{R_tot}) and predialytic relative volume overload was not interpretable.

12.7 Does Body Composition Confound the Calculation of Volume Overload?

12.7.1 Evaluation of Tissues

Anthropometry supported the adiposity parameters of the *Body Composition Monitor*, such as relative fat mass or adipose tissue mass, since the results of the two methods correlated well.

12.7.2 Influence of Body Composition on the Volume-Overload Equation

The ratio between extracellular and intracellular volume ($I_{ECW/ICW}$) is the most popular bioimpedance variable for the assessment of volume state. However, this ratio is strongly influenced by body tissue composition. Since $I_{ECW/ICW}$ is greater in adipose tissue, higher values are found in older and obese subjects. The model of *Chamney et al.* seems to overcome this obvious error, because the sizes of lean tissue and of adipose tissue are incorporated into its equation.

However, negative correlations between *Chamney's* relative volume overload and obesity markers were observed in the present study. Theoretical reasons which could explain inexact and wrongly low volume overload values in the obese patient group are presented in the following:

The trunk accounts for a small part of overall wrist-to-ankle resistance. Therefore, the tissue composition of the trunk is estimated to a high degree by the composition of the limbs. Hence, small

errors in the estimation of limb composition have large effects on overall body composition. In obese patients, the limbs represent an even smaller part of the body mass than in slim patients. Stochastic errors, in other words, the variability of results, will thus increase with body mass index. Against this background, the future development of wrist-to-ankle methods has to be questioned, because the obesity in general population will augment.

In obese patients, the shape of the trunk differs from the assumed proportions. Please refer to chapter 12.5.1.2 for a more detailed discussion of this item.

Other problems are directly related to the *Chamney Model* and to its underlying study, which was to evaluate the normal water volume fractions in tissues (19). The participants had to be healthy and covered a large range in body mass index, including obese subjects with a body mass index of 30 or more. It has to be questioned whether these obese subjects can be considered as healthy. Adiposity is not only a disease itself, but leads to pathologies, such as cardiac impairment, which cause volume overload. Supposing a volume overload in the obese patient group, water volume fraction of adipose tissue would be wrongly high. Please consider the high standard deviation of water volume fractions found in adipose tissue (the coefficient of variance was found to be 21.3 [%] for the water volume fraction of adipose tissue, whereas it was only 1.3 [%] for lean tissue values).

Furthermore, the *Chamney Model* assumes a constant ratio between extracellular and intracellular volumes in healthy tissues. In severely obese subjects, the fat tissue may have another structure with a larger intracellular compartment, since the volume of stored lipids per cell is larger, as argued by *Matthie* (10). The same publication, however, cited mechanisms with an opposing effect as well (greater extracellular compartment in the fat tissue of obese subjects).

All in all, the *Chamney Model* is an attempt to overcome errors in volume overload equation by taking tissue composition into account. However, equations are likely to be less accurate with an extreme body mass index.

12.8 Follow-up Study

Quick changes in mass are due to changes in volume state. Surprisingly, body mass change was better reflected by the changes of extracellular and total body water volume than by the evolution of *Chamney's* volume overload. However, even the volume overload of the *Chamney Model* was significantly related to body mass change. Furthermore, the reflection of volume change by *Chamney's* volume overload was satisfactorily demonstrated in a poster of *Wabel et al.* (55). Moreover, it is not for sure that volume changes were the sole reasons for mass changes. The fractions of adipose and lean tissues may have changed as well in the period of up to four weeks between the two study days. Blood pressure did not evolve in parallel to the volume state.

12.9 Conclusion

12.9.1 Overview of the Main Results

The following answers refer to the aims of the study as defined in chapter 9.3.

ad 1) Despite a partial exclusion of multimorbid subjects, the study population was representative.

ad 2) Volume indicators differ with respect to their sensitivity or specificity, to the assessment method chosen and to their implementation in clinical routine. A number of the confounders which have been described in literature were statistically linked to the volume indicators of the present study.

ad 3) The accuracy of predialytic volume indicators was confirmed by the strong relationships between these values. While some postdialytic values were related to each other, their accuracy could not be confirmed, since they reflected other volumes and were influenced by additional factors as compared with predialytic volume indicators.

Ad 4) Ad 4a) Ultrafiltration volume was related to the blood pressure drop, but not to the change of NT-pro BNP. Ad 4b) Surprisingly, there was a large discrepancy between clinical dry mass and the volume overload as obtained by bioimpedance spectroscopy and by other volume indicators.

Ad 5) Three hypotheses were proposed to explain the discrepancy found in 4b): poor clinical evaluation of dry mass, inaccuracy of the bioimpedance and/or non-achievement of volume targets because of comorbidity or side effects. None of these hypotheses could be totally confirmed or totally rejected: possible errors were identified on the different levels of the bioimpedance method used (measurement, *Cole Model*, *Chamney Model*). The comorbidity factors investigated could not explain the discrepancy found in 4b). Possibly, these factors were not sufficiently representative of the respective pathology.

Ad 6) The study design was not appropriate to investigate the relationship between volume state and haemodynamic parameters (cardiac output, peripheral resistance). Because of volume shifts during the dialysis procedure, blood volume could not be estimated at treatment end. Other factors with strong impact on cardiac index were identified (age, cardiac impairment, access flow).

Ad 7) For both theoretical and statistical reasons, the *Chamney Model* may be inaccurate at the extremes of body composition, in particular if adipose tissue mass is increased.

Ad 8) Body mass change was reflected by the change of water volumes derived from bioimpedance spectroscopy.

12.9.2 Limitations of the Present Study

Some limitations have already been discussed in the previous chapters. An overview of the main limitations: the present study was designed as a cross-sectional study. Such a study structure is not suited to distinguish between a causal factor and its consequence. The investigated patient sample was small and multimorbid subjects were underrepresented (selection bias). Estimation of blood volume at the end of the dialysis session was not possible. Consequently, volume state could not be compared to cardiac parameters which were assessed at treatment end. Cardiac characterisation, which consisted of cardiac index and NT-pro BNP only, was insufficient.

Already in the present study design, the blood volume at treatment beginning was reflected by the size of the extracellular compartment. By adding a haematocrit monitoring device like *CritLine*, the quantification of relative blood volume change during treatment would be possible. Theoretically, these two variables (predialytic blood volume, relative change of blood volume) make it possible to describe blood volume at treatment end. In fact, however, the absolute blood volume will not be estimated exactly enough, since the blood-to-extracellular-volume relationship is variable. The use of natriuretic peptides as markers of the actual blood volume is another possibility, but they are not accurate enough (43), in particular during or after treatment, as demonstrated above.

More promising is the following proposal: the moment of cardiac output measurement should be shifted from the end of the treatment (as in the present study design) to its beginning, when blood volume is reflected by extracellular volume.

In a longitudinal design, the changes of volume state and of cardiac output could be monitored, eliminating the impact of confounders, such as age and access flow.

Cardiac characterisation has to be more detailed. The following parameters would be easy to assess: troponin plasma levels, the number of cardiac events and a clinical classification of cardiac impairment as that of the *New York Heart Association*.

13 APPENDIX

13.1 Variables

13.1.1 Rules of naming

13.1.1.1 Introduction

Four levels of measurement were proposed by *Stevens* (15): nominal, ordinal, interval and ratio scale. Variable belonged to the class of ratio scale, unless mentioned otherwise. Variables were written in italic. The variable name consisted always of one capital letter, such as *M*, *A*, *C*. This letter was the abbreviation for the function of the variable: *M* represents, for example, *Mass*. The variables and the functions they represented are explained in the following paragraph:

Mass is the quantity of matter in a body. The scientific unit used was [kg]. *Length* corresponds to the distance between two points. *Length* was measured in [m]. *Area* is in mathematical terms the amount of surface. It was displayed as [m²]. *Volume* is the size, measure or amount of anything manifesting itself in three dimensions. *Volume* was measured in [L]. *Flow* is the volume of fluid that flows through a passage of any given section in a unit of time. *Flow* values had different units, the units' numerators represented volume, their denominators represented time, *e.g.* [L/min]. *Concentration* is a measure of the amount of dissolved substance contained per unit of volume, *e.g.* [pg/mL]. *Time* either corresponded to a point of time (as date and time of day) or it represented a period of time (duration). Duration values were scaled as ratio, points of time, however, should be displayed on an interval scale. *Frequency* is, generally spoken, the number of events, which are observed during a given period. In this text, the variables of *Frequency* corresponded always to heart rates, measured in [bpm]. *Pressure* was used as a short form for blood pressure; the scientific unit was always [mmHg]. *Index* was a value, which was divided by another value such as body area surface or mass, in order to render the value comparable between individuals. *Index* values had different scientific units. The term *Nominal* contained all non-numeric variables. The expression *Nominal* may be misleading, because *Nominal* contained not only nominal but also ordinal variables. These variables identified a specific patient or a specific group of patients: *e.g.* patients with moist râles (1st group) or patients without this symptom (2nd group).

Tab 13-1 Variable names

Variable	Explanation	Unit	Scale
P	*Pressure or blood pressure*	[mmHg]	Ratio
M	*Mass*	[kg]	Ratio
L	*Length*	[m]	Ratio

A	*Area*	[m²]	Ratio
V	*Volume*	[L]	Ratio
Q	*Flow*	*e.g.* [L/min]	Ratio
C	*Concentration*	*e.g.* [pg/mL]	Ratio
T	*Time*	various	Interval or ratio
F	*Frequency or heart rate*	[bpm]	Ratio
I	*Index*	various	Ratio
N	*Nominal*	no unit	Nominal or ordinal

13.1.1.2 Subscripts

The naming of subscripts responded to following rules:

1) Important subscripts were mentioned before less important ones.

2) Abbreviations were put in capital letter; short forms like *sys*, consisting of at least one syllable, were not considered as abbreviations and were consequently written in small letters.

3) If a subscript contained more than one expression, the expressions were connected by a underline. In the case that the following expression was a number, no underline nor space between the expressions was put.

4) An expression had to be unambiguous: thus the short forms for systolic and systemic were different: systolic was always represented by *sys*, whereas systemic had another short form (*system*).

5) The subscript were as short as possible, but sometime redundant letters were not eliminated, in order not to change common abbreviations; *e.g.* BMI for body mass index. The variable is named I_{BMI}, Although "index" is already indicated by the initial *"I"*.

13.1.2 List of All Variables

Tab 13-2 All variables in alphabetic order

Variable	Full name	Unit	Scale	Equation
A_{BSA}	*Body surface area (Du Bois equation)*	[m²]	Ratio	$0.2025 \cdot M_{pre}^{0.425} \cdot L_{height}^{0.725}$

C_{alb}	*Albumin*	[g/L]	Ratio	-
C_{BNP_change}	*Change between predialytic and postdialytic NT-pro BNP*	[pg/mL]	Ratio	$C_{BNP\_post} - C_{BNP\_pre}$
C_{BNP_post}	*Postdialytic NT-pro brain natriuretic peptide*	[pg/mL]	Ratio	-
C_{BNP_pre}	*Predialytic NT-pro brain natriuretic peptide*	[pg/mL]	Ratio	-
C_{chol}	*Total cholesterol*	[mg/dL]	Ratio	-
C_{HCO3_post}	*Postdialytic blood bicarbonate*	[mmoL/L]	Ratio	-
C_{HCO3_pre}	*Predialytic blood bicarbonate*	[mmoL/L]	Ratio	-
C_{HDL}	*High density lipoprotein*	[mg/dL]	Ratio	-
C_{LDL}	*Low density lipoprotein*	[mg/dL]	Ratio	-
$C_{natrium\_dialysate}$	*Sodium in the dialysate*	[mmoL/L]	Ratio	-
$C_{natrium\_serum}$	*Blood sodium*	[mmoL/L]	Ratio	-
$C_{protein\_total}$	*Total protein*	[g/L]	Ratio	-
C_{tri}	*Triglycerides*	[mg/dL]	Ratio	-
F_1, F_2, F_3,...	*1st, 2nd, 3rd,...intradialytic heart rate*	[bpm]	Ratio	-
F_{card}	*Heart rate during haemodynamic monitoring*	[bpm]	Ratio	-
F_{change}	*Change between predialytic and postdialytic heart rate*	[bpm]	Ratio	$F_8 - F_1$
F_{pre}	*Predialytic heart rate*	[bpm]	Ratio	-
I_{BMI}	*Body mass index*	[kg/m²]	Ratio	$\frac{W_{pre}}{L_{height}^2}$
I_{BNP_change}	*Relative change between predialytic and postdialytic NT-pro BNP*	[%]	Ratio	$100 \cdot \frac{C_{BNP\_change}}{C_{BNP\_pre}}$
$I_{BNP\_change/UFV}$	*Relative Change between Predialytic and Postdialytic NT-pro BNP at a given ultrafiltration volume*	[%/L]	Ratio	**Fehler! Textmarke nicht definiert.Fehler! Textmarke nicht definiert.Fehler! Textmarke nicht definiert.** $\frac{I_{BNP\_change}}{V_{UF\_real}}$
I_{card}	*Cardiac index*	[L/min/m²]	Ratio	$\frac{Q_{card}}{A_{BSA}}$

I_{card_mod}	*Cardiac index, modified*	[L/min/m²]	Ratio	$\frac{Q_{card\_mod}}{A_{BSA}}$
I_{card_system}	*Systemic cardiac index*	[L/min/m²]	Ratio	$\frac{Q_{card} - Q_A}{A_{BSA}}$
I_{CBVI}	*Central blood volume index*	[mL/kg]	Ratio	$1000 \cdot \frac{V_{CBV}}{W_{pre}}$
$I_{ECW/ICW}$	*Ratio between extracellular water volume and intracellular water volume*	[ ]	Ratio	$\frac{V_{ECW}}{V_{ICW}}$
I_{FAT}	*Relative fat tissue mass*	[%]	Ratio	$100 \cdot \frac{W_{FAT}}{W_{pre}}$
I_{FTI}	*Fat tissue index*	[kg/m²]	Ratio	$\frac{W_{FAT}}{L_{height}^2}$
$I_{LDL/HDL}$	*Ratio between low density lipoprotein and high density lipoprotein*	[ ]	Ratio	$\frac{C_{LDL}}{C_{HDL}}$
I_{P_change}	*Relative change between predialytic and postdialytic mean arterial pressure*	[%]	Ratio	$100 \cdot \frac{P_{change}}{P_{mean1}}$
I_{Q_UFV}	*Relative ultrafiltration rate*	[%/h]	Ratio	$100 \cdot \frac{Q_{UFV}}{V_{ECW}}$
I_{QA/Q_card}	*Ratio between access flow and cardiac output*	[ ]	Ratio	$\frac{Q_A}{Q_{card}}$
I_{R_system}	*Systemic peripheral resistance index*	[mmHg/L/m²]	Ratio	$\frac{P_{mean\_card}}{I_{card\_system}}$
I_{R_tot}	*Total peripheral resistance index*	[mmHg/L/m²]	Ratio	$\frac{P_{mean\_card}}{I_{card}}$
I_{UFV_deliv}	*Relative delivered ultrafiltration volume*	[%]	Ratio	$100 \cdot \frac{V_{UF\_deliv}}{V_{ECW}}$
I_{UFV_prescr}	*Relative prescribed ultrafiltration volume*	[%]	Ratio	$100 \cdot \frac{V_{UF\_prescr}}{V_{ECW}}$
I_{VO_post}	*Postdialytic relative volume overload*	[%]	Ratio	$100 \cdot \frac{V_{O\_post}}{V_{ECW} - V_{UF\_deliv}}$
I_{VO_pre}	*Predialytic relative volume overload*	[%]	Ratio	$100 \cdot \frac{V_{O\_pre}}{V_{ECW}}$
I_{WHR}	*Waist-to-hip ratio*	[ ]	Ratio	$\frac{L_{waist}}{L_{hip}}$
L_{height}	*Body height*	[m]	Ratio	-

L_{hip}	*Hip circumference*	[m]	Ratio	-
L_{MUAC}	*Mid upper arm circumference*	[m]	Ratio	-
L_{waist}	*Waist*	[m]	Ratio	-
M_{ATM}	*Adipose tissue mass*	[kg]	Ratio	-
M_{BCM}	*Body cell mass*	[kg]	Ratio	-
M_{dry}	*Dry mass*	[kg]	Ratio	-
M_{FAT}	*Fat tissue mass*	[kg]	Ratio	-
M_{LTM}	*Lean tissue mass*	[kg]	Ratio	-
M_{pre}	*Predialytic mass*	[kg]	Ratio	-
M_{treat_post}	*Postdialytic mass, measured for ultrafiltration treatment*	[kg]	Ratio	-
M_{treat_pre}	*Predialytic mass, measured for ultrafiltration treatment*	[kg]	Ratio	-
N_{AHD}	*Number of antihypertensive drugs*	[ ]	Ordinal	-
N_{cramps}	*Symptoms indicating cramps*	[0/1]	Nominal	$\begin{cases} 0 & \text{if } N_{sympt4} + N_{sympt5} = 0 \\ 1 & \text{else} \end{cases}$
N_{diab}	*Diabetic*	[Y/N]	Nominal	-
N_{edema}	*Œdema of the legs*	[Y/N]	Nominal	-
$N_{fatigue}$	*Symptoms indicating fatigue*	[0/1]	Nominal	$\begin{cases} 0 & \text{if } N_{sympt6} + N_{sympt7} = 0 \\ 1 & \text{else} \end{cases}$
$N_{hypotens}$	*Symptoms indicating hypotension*	[0/1]	Nominal	$\begin{cases} 0 & \text{if } N_{sympt2} + N_{sympt3} + N_{sympt8} = 0 \\ 1 & \text{else} \end{cases}$
N_{ID}	*Identification number*	[ ]	Nominal	-
$N_{membrane}$	*Type of dialysis membrane*	[ ]	Nominal	-
N_{moist}	*Moist râles*	[Y/N]	Nominal	-
N_{score}	*Wizemann's clinical volume score*	[ ]	Ordinal	$\sum_{x=sympt1}^{sympt16} N_x$
N_{sex}	*Gender*	[M/F]	Nominal	-
N_{side}	*Side of bioimpedance measurement*	[L/R],[S/N]	Nominal	-

N_{sympt1}, N_{sympt2}, N_{sympt3},...	*1st, 2nd, 3rd,...symptom of Wizemann's score*	[≥-6/≤4]	Ordinal	-
P_{change}	*Change between predialytic and postdialytic mean arterial pressure*	[mmHg]	Ratio	$P_{mean8} - P_{mean1}$
P_{change_dia}	*Change between predialytic and postdialytic diastolic pressure*	[mmHg]	Ratio	$P_{dia8} - P_{dia1}$
P_{change_sys}	*Change between predialytic and postdialytic systolic pressure*	[mmHg]	Ratio	$P_{sys8} - P_{sys1}$
P_{dia_card}	*Diastolic blood pressure during haemodynamic monitoring*	[mmHg]	Ratio	-
P_{dia_pre}	*Predialytic diastolic blood pressure*	[mmHg]	Ratio	-
P_{dia1}, P_{dia2}, P_{dia3},...	*1st, 2nd, 3rd,... intradialytic diastolic blood pressure*	[mmHg]	Ratio	-
P_{mean_card}	*Mean arterial pressure during haemodynamic monitoring*	[mmHg]	Ratio	$P_{dia\_card} + ⅓\cdot(P_{sys\_card} - P_{dia\_card})$
P_{mean_pre}	*Predialytic mean arterial pressure*	[mmHg]	Ratio	$P_{dia\_pre} + ⅓\cdot(P_{sys\_pre} - P_{dia\_pre})$
P_{mean1}, P_{mean2}, P_{mean3},...	*1st, 2nd, 3rd,... intradialytic mean arterial pressure*	[mmHg]	Ratio	$P_{dia1} + ⅓\cdot(P_{sys1} - P_{dia1})$, $P_{dia2} + ⅓\cdot(P_{sys2} - P_{dia2})$, $P_{dia3} + ⅓\cdot(P_{sys3} - P_{dia3})$,...
P_{pulse_card}	*Pulse pressure during haemodynamic monitoring*	[mmHg]	Ratio	$P_{sys\_card} - P_{dia\_card}$
P_{pulse_pre}	*Predialytic pulse pressure*	[mmHg]	Ratio	$P_{sys\_pre} - P_{dia\_pre}$
P_{pulse1}, P_{pulse2}, P_{pulse3},...	*1st, 2nd, 3rd,... intradialytic pulse pressure*	[mmHg]	Ratio	$P_{sys1} - P_{dia1}$, $P_{sys2} - P_{dia2}$, $P_{sys3} - P_{dia3}$,...
P_{sys_card}	*Systolic blood pressure during haemodynamic monitoring*	[mmHg]	Ratio	-
P_{sys_pre}	*Predialytic systolic blood pressure*	[mmHg]	Ratio	-
P_{sys1}, P_{sys2}, P_{sys3},...	*1st, 2nd, 3rd,... intradialytic systolic blood pressure*	[mmHg]	Ratio	-
Q_A	*Access flow*	[L/min]	Ratio	-
Q_{card}	*Cardiac output*	[L/min]	Ratio	-

Q_{card_mod}	*Cardiac output, modified*	[L/min]	Ratio	$Q_{card} - 0.564 \cdot Q_A^3 + 2.1964 \cdot Q_A^2 - 3.8863 \cdot Q_A$
Q_{UFV}	*Ultrafiltration rate*	[L/h]	Ratio	$\frac{V_{UF\_deliv}}{T_{duration}}$
R_{QA}	*Access resistance*	[mmHg/L]	Ratio	$\frac{P_{mean\_card}}{Q_A}$
R_{system}	*Systemic peripheral resistance*	[mmHg/L]	Ratio	$\frac{P_{mean\_card}}{Q_{card} - Q_A}$
R_{tot}	*Total peripheral resistance*	[mmHg/L]	Ratio	$\frac{P_{mean\_card}}{Q_{card}}$
T_{age}	*Age*	[years]	Interval	-
T_{before_end}	*Period between haemodynamic monitoring and treatment end*	[h]	Ratio	$T_{end} - T_{card}$
T_{card}	*Time of haemodynamic monitoring*	[h]	Interval	-
T_{date}	*Date*	[ ]	Interval	-
$T_{duration}$	*Duration of ultrafiltration treatment*	[h]	Ratio	$T_{end} - T_{start}$
T_{end}	*End of ultrafiltration treatment*	[h]	Interval	-
T_{P_card}	*Time of blood pressure measurement for haemodynamic monitoring*	[h]	Interval	-
T_{P1}, T_{P2}, T_{P3},...	*Time of 1st, 2nd, 3rd,... intradialytic blood pressure measurement*	[h]	Interval	-
T_{start}	*Start of ultrafiltration treatment*	[h]	Interval	-
V_{CBV}	*Central blood volume*	[L]	Ratio	-
V_{ECW}	*Extracellular water volume*	[L]	Ratio	-
V_{ICW}	*Intracellular water volume*	[L]	Ratio	-
V_{O_post}	*Postdialytic volume overload*	[L]	Ratio	$V_{O\_pre} - V_{UF\_deliv}$
V_{O_pre}	*Predialytic volume overload*	[L]	Ratio	-
V_{resid_urine}	*Residual urine*	[L]	Ratio	-
V_{SV}	*Stroke volume*	[L]	Ratio	-
V_{tot}	*Total body water volume*	[L]	Ratio	-

V_{UF_deliv}	*Delivered ultrafiltration volume*	[L]	Ratio	-
V_{UF_prescr}	*Prescribed ultrafiltration volume*	[L]	Ratio	$M_{treat\_pre} - M_{dry}$
V_{watson}	*Total body water volume, estimated by Watson Equation*	[L]	Ratio	Male: $2.447 - 0.09156 \cdot T_{age} + 10.74 \cdot L_{height} + 0.3362 \cdot M_{pre}$ Female: $-2.097 + 10.69 \cdot L_{height} + 0.2466 \cdot M_{pre}$

13.2 Case Report

ID		ID= f.e. 01XY2
Date		

age		years
gender		M/F
diabetes		Y/N

Anthropometric

weight(pre)		kg
height		cm
waist		cm
hip		cm
MUAC		cm

On Examination

edema of the leg		Y/N
moist rales		Y/N

Blood Pressure (pre)

BP sys(pre)		mmHg
BP dia(pre)		mmHg
heart rate(pre)		bpm

Body Composition

OH		L
TBW		L
ECW		L
ICW		L
LTM		kg
FAT		kg
ATM		kg
BCM		kg
which arm?		L/R,S/N

Dialysis Treatment

UF volume calc		L
UF volume real		L
dialysate Na+		mmol/L
start		h:min
end		h:min
dialysis membrane		
HCO3(pre)		mmol/L
HCO3(post)		mmol/L
weight treat(pre)		kg
weight treat(post)		kg
residual urine		L

Blood pressure (intradialytic)

	time	BP sys	BP dia	heart rate
id1				
id2				
id3				
id4				
id5				
id6				
id7				
id8				
idt				

Clinical Score Hydration

Thirst directly after HD		-1
Sympt. BP decrease, position change		-1
Sympt. BP decrease, saline infusion		-2
Muscle cramps, moderate (calf)		-2
Muscle cramps, severe (calf)		-3
Tiredness betw. dialyses		-3
Dizziness between dialyses		-4
Sympt. hypotension, vomiting		-6
No symptoms		0
BP increase during UF		2
Pretibial edema, weak		2
Chronic coughing		2
Dyspnoea at rest, recumbent		2
Pretibial edema, severe		3
Dyspnoea at rest, one cushion		3
Dyspnoea at rest, two cushions		4

Antihypertensive Medication

Clonidine		mg
Nifedipine		mg
Nitrendipine		mg
Diltiazem		mg
Felodipine		mg
Isradipine		mg
Amlodipine		mg
Doxazosin		mg
Carvedilol		mg
Metoprolol		mg
Dihydralazine sulfate		mg
Ramipril		mg
Enalapril		mg
Enalapril+HTC		tbl.
Eprosartan		mg
Valsartan		mg
Losartan		mg
Moxonidine		mg
Candesartan		mg

Number of AH	

Transonic

	1st	2nd	mean	
CO				L/min
CBV				L
access flow				mL/min
time(measurem)				h:min

Lab

serum Na+		mmol/L
total protein		g/L
albumin		g/L
Tri		mg/dL
Chol		mg/dL
LDL		mg/dL
HDL		mg/dL
NT-proBNP(pre)		pg/mL
NT-proBNP(post)		pg/mL

14 CURRICULUM VITAE

Personal information

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Education and training

1990-1995	Primary school in Nonntal, Salzburg City
1995-2003	Borromäum, a private secondary school in Salzburg City
10/2003-9/2004	“Civilian service” (instead of military service) at the Salzburg University Hospital
since 2004	Studies of Medicine at the Medical University of Graz
08/2007-06/2008	Université Montpellier 1, France, under the ERASMUS exchange programme

since 05/2009 Work on the thesis “Body Composition in Haemodialysis Patients”

since 12/2009 Université Louis Pasteur, Strasbourg, France, under the Student Practical Placement ERASMUS exchange programme

Internship

Since 2004 The new curriculum of Medicine in Graz includes various internships in hospital during the academic year from the first year of studies.

2006-2009 18 additional weeks of internship (40 hours per week) in hospitals during summer holidays

2007-2008 Nine months of internship (20 hours per week) in Montpellier during the academic year

since 10/2009 Practical year with internships in general medicine (Weiz, Austria) at the dermatology respectively accident and emergency departments (both in Strasbourg, France) and in internal medicine (Montpellier, France)

Personal skills and interests

Languages Mother tongue: German

Other languages: advanced knowledge of English and French, basic knowledge of Spanish and Japanese

Medical English: attending the course “MB5: Anglais” (15 units of 120 minutes) in Montpellier, France; attending “Basic Medical Communication II” and “Basic Medical English II” in Graz

General interests

Sports as hiking, bicycling, oarsmanship, swimming, volley ball

Cinema: writing film criticism for an Austrian web page

Music: Post Punk, British Pop, Alternative Rock

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