The role of technological advances in sodium prescription and adequacy assessment during hemodialysis

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**The role of technological advances in sodium
prescription and adequacy assessment during
hemodialysis**

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The role of technological advances in sodium prescription and adequacy assessment during hemodialysis

PROEFSCHRIFT

Ter verkrijging van de graad van doctor
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Karin Elisabeth Maria Moret
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Promotor:

Prof. dr. K.M.L. Leunissen

Copromotores:

Dr. J.P. Kooman

Dr. C.H. Beerenhout, Maxima Medisch Centrum, Veldhoven

Beoordelingscommissie:

Prof. dr. A.P.G. Hoeks (voorzitter)

Dr. P.J. Blankestijn, UMC Utrecht

Prof. dr. J.P. van Hooff

Prof. dr. R.P. Koopmans

Dr. P. Kotanko, Renal Research Institute, New York

Voor Papa

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Chapter 1

Introduction

**The role of technological advances in sodium prescription
and adequacy assessment during hemodialysis**

Introduction

The role of technological advances in sodium balance and urea removal during hemodialysis

Regulation of water and electrolyte balance and excretion of uremic waste products belong to the predominant functions of the kidney. In patients with end-stage renal failure, dialysis has to substitute for these functions.

The most frequently used method for chronic dialysis treatment is hemodialysis. During hemodialysis, blood is separated from dialysis fluid, a highly purified solution with a mix of electrolytes and bicarbonate, by a semi permeable membrane (the dialyzer). During hemodialysis, uremic waste products and excess electrolytes, such as potassium, are removed by diffusion from the blood to the dialysis fluid, whereas water is removed by ultrafiltration (which occurs by application of a hydrostatic pressure gradient over the dialyzer). Hemodialysis is generally performed for a minimum of 3 times per week, 4-5 hours per treatment. During this treatment blood flows at a rate of 300 ml/min, whereas dialysis fluid flows, counter currently, at a rate of 500 ml/min or higher.

This thesis focuses on these two major issues which, even after nearly 50 years of chronic dialysis therapy, still remain a subject of controversy in the literature, i.e. the regulation of sodium balance as well as the monitoring of dialysis adequacy in terms of urea removal.

Especially, the role of recent technological advances in monitoring and prescribing

1. **sodium balance** during hemodialysis, as well as
2. **dialysis adequacy** will be the scope of investigation.

1 Sodium balance during hemodialysis

Sodium and water loading in dialysis patients

One of the main tasks of the kidney is to regulate sodium and water homeostasis, which it performs by a fine-tuned balance between filtration, reabsorption and secretion. In patients with end stage renal failure treated with hemodialysis, this complex role of the kidney is substituted by an artificial extracorporeal system. This is not an easy task given the fact that the normal kidney is working continuously (168 hours per week). The artificial system has to equalise this task in 12-15 hours per week. The removal of relatively large amounts of water and sodium in such a short period of time may contribute to intra-dialytic hypotensive episodes, which is a serious limitation in the realization of “dry weight”. Moreover, adherence to a sodium restricted diet, which might aid in reducing inter-dialytic weight gain, is often difficult for dialysis patients to maintain, also given the fact that sodium is present in many prefabricated foods¹.

It is therefore not surprising that volume overload is very common in hemodialysis patients². This chronic volume overload plays a major role in the pathogenesis of hypertension and subsequently left ventricular hypertrophy in dialysis patients³. Recently, overhydration was shown to be directly related to mortality in dialysis patients⁴.

The main effect of a high dietary salt intake on blood pressure and volume control in dialysis patients may be mediated by an increase in plasma osmolality and thirst, leading to increased fluid intake. However, there are also arguments for an independent effect of sodium on blood pressure control and cardiovascular structure and functioning in patients with end stage renal failure. This may be related to disturbances in activity and or response to various neurohumoral changes, such as the renin-angiotensin and sympathetic nervous systems, Na-K-ATP-ase inhibitors, and the nitric oxide system in patients with end-stage renal failure^{5,6}.

The presence of an “osmotically inactive” sodium pool has recently been the focus of interest, although these observations have not yet been extrapolated to clinical practice⁷. Also, the relative importance of the volume independent pressor effects of sodium in patients with end stage renal disease is still not yet completely elucidated^{6,7}. Nevertheless, it is well known that a sodium restricted diet is of great importance in the treatment of hypertension and may finally result in reduction of left ventricular hypertrophy in dialysis patients⁸. However, the dialysis treatment itself plays also a very important role in sodium balance during dialysis.

Sodium removal during dialysis: theoretical considerations

During dialysis, sodium transport over the dialyzer occurs both by convection as well as by diffusion. The relative magnitude of convection is, in general, higher as compared to diffusion, although data on this subject are limited in the literature.

Given the high importance of volume and sodium homeostasis in hemodialysis patients, there are surprisingly few data on sodium balance during dialysis. This might be partly due to the complexity of the subject. Sodium flux across the dialyzer is dependent on various factors, such as the rate and amount of ultrafiltration, the difference between the ionized sodium concentration in plasma water and dialysate, the concentration of sodium in dialysate and the Donnan factor (the attractive force for positive ions by the negative loading of plasma proteins which cannot pass the dialysis membrane)⁹.

Sodium concentrations may be measured either in plasma or in plasma water, by different methods such as flame photometry, indirect ionometry and direct ionometry. The use of these different measure methods makes it difficult to compare studies. Additionally there is no consensus in what the preferred measuring method of sodium in plasma is, which makes the literature on this subject somewhat complicated.

The amount of sodium removed by convection is related to the volume of water removed during ultrafiltration, i.e. more or less equal to the product of the ultrafiltration volume and plasma sodium concentration. Due to the Donnan effect, the sodium concentration in the ultrafiltrate may be somewhat lower than the sodium concentration in plasma water^{9,10,11}, although large ultrafiltration volumes do not necessarily change the so-called "hydrosodium balance" (the relation between sodium and water in the body)¹⁰.

The principle of sodium removal by diffusion is more complicated. Diffusion of sodium between blood and dialysate is dependent on the sodium concentration in plasma water and in dialysate. Under normal circumstances, sodium concentration in plasma water is approximately 7% (approximately 10 mmol/l) higher as compared to the concentration in plasma, due to the fact that the volume of plasma is higher than the volume of plasma water. This is caused by the fact that $\pm 7\%$ of plasma consists of plasma proteins. As proteins are not present in dialysate, a relatively large diffusion of sodium from patient to dialysate would be expected if sodium concentration in dialysate would equal plasma sodium concentration^{9,10}. However, diffusion of sodium from patient to dialysate is hampered by the Donnan effect, i.e. the attraction of positively loaded ions by the negatively charged plasma proteins. The extent of the Donnan effect has been estimated around 5-10 mmol/l¹¹. Also the binding of sodium with anions which might reduce the sodium "activity" available for diffusion¹⁰, may be somewhat higher in plasma as compared to dialysate. In plasma water, it is assumed that ± 7 mmol/l of the total sodium concentration of ± 150 mmol/l sodium is in a bound form versus ± 4 mmol/l in dialysate^{9,10}.

Locatelli et al. showed that no net diffusive sodium transport between blood and dialysis fluid occurs when sodium concentration in plasma, as measured by flame photometry, is ± 2 mmol/l lower than sodium concentration of dialysate. This roughly corresponds to a difference in sodium activity between plasma water and dialysate of 4 mEq/l and to a Donnan effect in hemodialysis of 0.97⁹. These findings are in

agreement with those of van Stone et al, who observed “isonatremic” dialysis treatments (i.e. no change in the hydrosodium balance) when the sodium concentration in the dialysate was 2% higher as compared to the plasma sodium concentration^{12,13}.

On the other hand, Flanigan showed net sodium gain when a patient with a plasma sodium concentration of 138 mmol/l was dialyzed against a dialysate sodium concentration of 140 mmol/l. The different findings between these studies might be due to the fact that the Donnan effect is not completely predictable due to coating of proteins of the dialysis membrane^{11,12}. It can be expected that diffusive influx of sodium might occur with supraphysiologic dialysate sodium concentrations and in patients with low predialytic plasma sodium concentrations^{13,14}. However, exact data on sodium balance during dialysis are surprisingly scarce in the literature.

How can sodium balance be measured during dialysis?

Sodium removal during dialysis therapy can be assessed by measuring sodium concentration in the fresh dialysis fluid and the spent dialysate (direct dialysis quantification) by the following formula:

$$V_{\text{out}} \times C_{\text{out}} - V_{\text{in}} \times C_{\text{in}}, \text{ in which}$$

V_{out} = volume of spent dialysate,

C_{out} = concentration of solute in spent dialysate,

V_{in} = volume of fresh dialysate,

C_{in} = concentration of solute in fresh dialysate^{14,15}.

This impractical approach is only feasible for research purposes (collection of ± 120 litres of dialysate per treatment in a container at the dialysis unit) and not useful for daily clinical practice. Sodium removal (or intake) may also be reflected by changes in body weight and intradialytic (or, respectively, interdialytic) changes in plasma water sodium concentration by the following formula^{17,18}:

$$\begin{aligned} &= \text{predialysis total body sodium} - \text{postdialysis total body sodium} \\ &= \text{predialysis plasma sodium} \times ((0.58 \times \text{target weight}) + \text{ultrafiltration volume}) \\ &\quad - \text{postdialysis plasma sodium} \times (0.58 \times \text{target weight}) \end{aligned}$$

However, this formula assumes that total body water is 58% of body weight in dialysis patients, which is not necessarily correct in (all) dialysis patients¹⁹.

Additionally, although both methods are basically physiologically sound, it is hampered by the variability of the different sodium measurements. It has been stated that an acceptable level for the variation coefficient of flame photometry and ion-selective electrodes is 1.0 and 1.4%, respectively^{20,21}. Although this is quite acceptable for clinical purposes, a difference of 2.8 mmol/l between pre- and post plasma sodium concentration might reflect a major change in the hydrosodium balance, but might also be entirely explained by a variation in the methodology. Sodium removal during hemodialysis can also be estimated with single-pool kinetics, for which successful

models have been developed²²⁻²⁴. Although not easily applied to daily clinical practice due to their complexity, these models played an important role in the development of measurement and feedback systems which are able to measure and model plasma conductivity, and assess ionic mass balance during hemodialysis (see below).

How to measure sodium in plasma and dialysate?

When discussing sodium concentration in plasma and dialysate, it is important to reflect shortly on the different methods available to measure sodium. It is important to distinguish between sodium concentration and sodium activity. Whereas the sodium concentration reflects the total amount of sodium divided by the distribution volume, sodium activity refers to ionic activity, which is the relevant fraction for diffusion^{2,7,10}.

Flame photometry is based on the principle that each element has its own specific spectrum of emission. After excitation, by an increase in temperature, electrons are transferred from a lower to a higher energy state. After returning to the lower energy state, the electrons emit a photon with a characteristic wavelength, which may correspond to a colour in the visible spectrum (e.g. yellow in case of sodium). Using flame photometry to detect plasma sodium, the change in intensity of a flame color after introduction of a plasma sample is assessed. Flame photometry measures total sodium concentration (i.e. the ionic concentration plus the amount bound with anions) in a plasma sample with a known volume. Normally plasma consists for 93% of water and for 7% of proteins and lipids. Thus, as flame photometry measures sodium in a sample of plasma (and not of plasma water), spuriously low plasma levels may be reported if the concentration of proteins or lipids in plasma increases (pseudohyponatremia). In dialysate, the flame photometry measures total sodium concentration, and due to the absence of significant proteins, pseudohyponatremia is not a concern.

In contrast to flame photometry, direct ionometry measures sodium activity in plasma water, irrespectively of the volume in which sodium is dissolved. The sodium activity is converted into sodium concentration using the activity coefficient of the solution¹¹. Due to the fact that 6-7% of the volume in plasma is taken by lipids and proteins (see above), the concentration of sodium in plasma water is 6-7% higher as compared to the concentration in plasma (i.e. ± 149 -150 mmol/l as compared to 140 mmol/l). Sodium activity may be lower than the actual concentration due to the bonding of sodium with anions such as bicarbonate. Also in dialysate, sodium activity is lower (± 4 mmol/l) as compared to the sodium concentrations due to bonding of sodium with anions such as bicarbonate. Therefore, sodium concentration values reported in dialysate by direct ionometry may be lower as compared to the values of flame photometry²⁵.

Many laboratories use indirect ionometry to measure sodium in plasma and dialysate. Using indirect ionometry, a sample of plasma (not plasma water) is diluted and all

sodium present in the sample is ionized due to addition of a buffer, which brings the activity coefficient nearly to 1.0. Therefore indirect ionometry reflects the total sodium concentration in plasma and dialysate, and its values are comparable to those of flame photometry^{25,26}. The fact that the concentration is expressed in a known sample of plasma (instead of in plasma water, as with direct ionometry) also means that with indirect ionometry, pseudohyponatremia can occur, a phenomenon that is not observed with direct ionometry.

The use of different measurements of sodium concentration may thus have an effect on the assessment of sodium removal during dialysis, when using dialysate collections. In peritoneal dialysis, it has been shown that due to the bonding of sodium with anions in the dialysate in the course of a dwell (again: the complex is not measured), direct ionometry may underestimate sodium removal during dialysis as compared with flame photometry, whereas indirect ionometry yields results comparable to flame photometry²⁵. The different methods to estimate sodium removal have not been compared yet during hemodialysis. However, as the concentration of e.g. bicarbonate in the dialysate may change during the course of the dialysis treatment, it is likely that the use of direct ionometry to assess sodium balance by direct dialysis quantification would also lead to different values as compared to flame photometry or indirect ionometry.

In order to gain more insight into sodium balance during hemodialysis, frequent assessment of plasma sodium is mandatory. However, this is complicated by the need for blood sampling. Therefore, there is a need for reliable, non-invasive methodology by which plasma sodium and sodium balance can be assessed on a treatment-to-treatment basis.

Conductivity and ionic mass balance measurements in the assessment of sodium balance

Conductivity of a solution is the ability to conduct an electrical current. In a watery solution, conductivity is related to ion content. It has been shown that a linear relation exists between the sodium content and conductivity of dialysate and plasma (water)^{27,28,29}. Therefore, it has been postulated that conductivity can substitute for sodium concentration in plasma and dialysate²⁷. Plasma conductivity (PC) can be assessed non invasively by measurement of ionic dialysance (D). In turn, ionic dialysance is assessed by measurement of dialysate conductivity at the dialyzer inlet ($C_{d,in}$) and outlet ($C_{d,out}$) after changing the dialysate inlet concentration (i.e. the smaller the change in conductivity at the dialysate outlet after changing the dialysate inlet concentration, the higher the ionic dialysance, due to transport over the dialyzer).

Figure 1.1 Scheme of the record of the inlet and outlet dialysate conductivity during a measurement of ionic dialysance where X_1 and X_2 are the two given values of inlet dialysate conductivity, Y_1 and Y_2 the two measured values of outlet dialysate conductivity and C_p the representation of the patient's plasma conductivity. Q_d is dialysate flow, Q_f ultrafiltration rate.

The conductivity model does not need to take the Donnan effect into account, because conductivity is determined by both positive and negative ions in the solution²⁵. As will be discussed later, the conductivity kinetic model can substitute for the sodium kinetic model in predicting post-dialytic plasma conductivity (as a substitute for sodium).

With the Diascan module in the Hospal Integra device, plasma conductivity (PC) is calculated by measuring ionic dialysance (D) in combination with dialysate flow (Qd) and dialysate conductivity measurements at the dialyzer inlet (C_{din}) and outlet (C_{dout}), according to the formula:

$$PC = [C_{dout} - (1 - D/Q_{din}) \times C_{din}] / (D/Q_{din}).$$

D is assessed every 30 min during dialysis treatment by measuring the increase in C_{dout} after a temporary increase in C_{din} by 1 mS/cm according to the formula:

$$D = (Q_{din} + Q_f) \times [1 - (C_{dout1} - C_{dout2}) / (C_{din1} - C_{din2})]^{27,28,30}.$$

1 and 2 indicate, respectively measurements before and after the temporary increase in C_{din} respectively, Q_{din} is dialysate flow at inlet and Q_f is ultrafiltration rate.

Empirically, plasma sodium was shown to be approximately 4 mmol/l lower than PC multiplied by 10^{27} , whereas sodium concentration in plasma water is slightly higher than $PC \times 10^{28}$. As will be discussed later, ionic dialysance is strongly related to urea clearance, and therefore this method has also been introduced for assessment of dialysis adequacy.

In addition, sodium balance can be approximated by assessing ionic mass balance (IMB) by constant measurement of the conductivity in the dialysis outlet and inlet according to the formula:

$$\text{IMB} = [(Qd_{\text{out}} \times Cd_{\text{out}}) - (Qd_{\text{in}} \times Cd_{\text{in}})] \times 10 \times \text{time (min)}$$

Qd_{out} = dialysate flow at outlet

Cd_{out} = dialysate conductivity at outlet

Qd_{in} = dialysate flow at inlet

Cd_{in} = dialysate conductivity at inlet

Although the sodium concentration is by far the greatest determinant of dialysate conductivity²⁹ the transfer of other ions such as potassium or bicarbonate might also influence ionic mass removal during dialysis.

The relation between sodium removal (estimated from pre- and postdialytic plasma sodium measurements, using the formula described above) and ionic mass balance was assessed by Lambie et al. The r^2 between both methods was 0.66 whereas IMB underestimated sodium loss by $14.8 \pm 3.3\%$ compared to the reference method. Still, also the inherent variation in plasma sodium measurements (see above) should be taken into account when assessing sodium balance by means of pre- and post-dialytic plasma sodium concentrations. Until now, IMB has not yet been validated using direct dialysis quantification.

The use of dialysate sodium in clinical practice

During dialysis, water and sodium are removed by controlled ultrafiltration resulting from the application of a hydrostatic gradient over the dialyzer. In contrast, due to their structure (the small surface area and the lack of permeability of the membrane), early dialysis systems were incapable of controlled ultrafiltration³¹. Water and sodium were removed by osmotic ultrafiltration, by using a high concentration of glucose in the dialysate (comparable to the ultrafiltration mechanism of peritoneal dialysis), in combination with a low sodium concentration of the dialysate (126 mmol/l). Dialysis treatment time in the earlier days of dialysis was much longer compared to the current policy of time (often > 8 hours/treatment versus 3 to 4 hours/treatment). The improved design of the dialyzer, blood pumps, and negative pressure dialysis modules, made removal of sodium and water by controlled ultrafiltration possible. Solute clearance was increased by using larger dialyzer surface areas, which permitted shortened dialysis times. The high clearance of uremic solutes resulted in rapid changes in plasma osmolality. This provoked the so-called dialysis disequilibrium syndrome, characterized by fatigue, nausea, muscle cramps and, in severe cases, brain oedema due to water transport from extracellular to intracellular compartment. In order to prevent the disequilibrium syndrome, and because low sodium dialysate was no longer necessary for sodium and water removal, dialysate sodium concentration was increased gradually to 130-135 mmol/l in the early eighties¹⁰, which reduced the

osmotic shift of water from the extracellular to the intracellular compartments. However, due to the decrease in dialysis time to approximately 4 hours, water and sodium had to be removed in a shorter time period, resulting in an increased risk of episodes of intra-dialytic hypotension.

A decline in blood volume during hemodialysis plays an important role in the pathogenesis of intra-dialytic hypotension. The decline in blood volume during dialysis is a resultant of the ultrafiltrated volume and refill from the interstitial compartments. With increased dialysate sodium concentrations, fluid shifts from the intracellular compartments to the extracellular and intravascular compartments is increased. This has led to the prescription of higher dialysate sodium concentrations. In a recent survey of Davenport et al. in 439 chronic dialysis patients, 251 were treated with a dialysate sodium concentration of 140 mmol/l, 132 with a concentration of 137-139 mmol/l, and 52 with a concentration of 136 mmol/l³². In the Netherlands* also different dialysate sodium concentrations are used in clinical practice:

*In general, dialysate conductivity of 14.0 mS/cm corresponds approximately to dialysate sodium concentration of 140 mmol/l with standard dialysate bicarbonate concentration of 34 mmol/l. In case of higher or lower dialysate bicarbonate concentration the conductivity will slightly differ

Dialysate sodium as a tool to prevent intra-dialytic hypotension

Despite changes in dialysis prescription, such as the use of lower dialysate temperatures, the appearance of intra-dialytic hypotensive episodes in dialysis patients is still regularly. Intra-dialytic hypotension not only results in patient discomfort but also may increase the risk of myocardial and cerebral ischemia³³. Probably due to an improved refill of plasma volume by increasing tonicity of the extracellular compartment, the use of high dialysate sodium concentrations (>144 mmol/l) resulted in a reduction in intra-dialytic hypotension in some^{34,35}, but

not in all studies³⁶. A beneficial effect on hemodynamic stability during dialysis was also observed for sodium profiles, in which dialysate sodium is modelled (most often from values up to 150 mmol/l at the start of dialysis to 140 mmol/l at the end of dialysis)^{34,37}. Various studies found a reduction in intra-dialytic hypotension with the use of sodium profiles^{34,37,38} which are also mentioned as a therapeutic option by K-DOQI guidelines³⁹.

However, sodium profiles may not be effective in all patients with frequent intra-dialytic hypotension⁴⁰. Unfortunately the use of both, high sodium dialysate and sodium profiles may lead to increased thirst, inter-dialytic weight gain, and hypertension^{36,38,40,41}. Few studies have addressed this long term effect of sodium profiles on sodium balance and plasma sodium concentration in dialysis patients. Therefore, the use of sodium profiles in the prevention of intra-dialytic hypotension is still a matter of controversy³³.

Individualization of dialysate sodium, variation in plasma sodium concentration

In order to prevent possible patient discomfort due to either diffusive sodium loading from dialysate to patient (cellular overhydration) or excessive diffusive sodium loss (intradialytic hypotension), individualization of the dialysate sodium might be a solution. This so-called zero hydrosodium balance causes removal of the exact quantity of sodium that has accumulated in the inter-dialysis period to reach a zero balance⁴². Prescribing dialysate sodium as the plasma sodium concentration was found to improve both hemodynamic stability during dialysis as well as inter-dialytic blood pressure control⁴³. For the prescription of individualized sodium dialysis, the pre-dialytic plasma concentration has to be known⁴⁰. Therefore the use of individualized sodium prescription would be facilitated if pre-dialytic plasma sodium was found to be a stable entity.

Indeed, a fixed sodium set point is assumed by various authors^{11,44,45}. Although pre-dialytic plasma sodium appeared to be relatively stable in a small study of Flanigan et al., the coefficient of variation in a cohort of non-diabetic dialysis patients during 12 consecutive months was 2%. Whereas this appears small, it corresponds to a range of 137-143 mmol/l in a patient with a mean pre-dialytic plasma sodium concentration of 140 mmol/l, which may have a major effect on diffusive sodium balance during dialysis, as discussed previously. At this moment, few studies assessed the variability of pre-dialytic plasma sodium concentrations in dialysis patients. Also, the relation between variations in plasma sodium and clinical parameters, such as inter-dialytic weight gain and blood pressure, has not been assessed.

On-line feedback models to control plasma conductivity and blood volume

In 1980, Gotch²³ developed a single-pool sodium kinetic model for hemodialysis (HD) in order to obtain a zero sodium balance over the treatment cycle (intra-HD sodium removal = inter-HD sodium accumulation). Using flame photometry to determine total sodium concentrations, this early analytical single-pool kinetic model showed a degree of imprecision of ~2.8 mmol/l in predicting end-dialysis plasma water sodium concentration. This means, for a final total body water volume of 40 litres (58% for 70 kg body weight), an imprecision of ~112 mmol in predicting sodium removal with dialysis. However, on the basis of Gotch's theoretical premises, Di Filippo⁴⁶ demonstrated more recently, using direct ionometry, a level of imprecision in the prediction of sodium balance of less than 34 mmol. Unfortunately, these models are unsuitable for routine clinical use because of the need for blood sampling and laboratory determinations at each dialysis session.

Recently, it has become possible to model the decline in blood volume and changes in plasma conductivity (PC), as a surrogate of plasma sodium, by means of feedback technologies. Following the theoretical premises of conductivity monitoring; i.e. dialysate and plasma sodium are linearly related to conductivity, a conductivity kinetic model can be used instead of a sodium kinetic model, which can be achieved by a dialysis module which is able to measure dialysis conductivity and ionic dialysance on-line, by which plasma conductivity can be assessed and modelled^{47,48}.

In the case of PC-controlled feedback, a target for end-dialytic PC is set, which is achieved by frequent adjustments of dialysate conductivity during the dialysis sessions, in response to on-line measured changes in PC^{29,49,50}. With PC-controlled feedback (Diacontrol®; Hospal-Gambro, Mirandola, Italy), PC is modelled automatically during dialysis by adjustment of DC using single-pool kinetic modelling. With PC-controlled feedback, it is possible to achieve these targets with a high level of precision. Post-dialytic plasma conductivity can be assessed with a precision of <0.14 mS/cm (~1.4 mmol/l)⁴⁷. Unfortunately, clinical experience with conductivity-controlled feedback in particular is still limited^{50,51}. In one study in patients treated with paired filtration dialysis (a modification of haemodiafiltration in which convection and diffusion take place separately) conductivity controlled feedback resulted in a decline in incidence in intra-HD hypotension⁵¹. Comparable results were reported in patients treated with hemodialysis, although these studies have only been published in abstract form^{52,53}. These results are nevertheless promising, but the effect of conductivity controlled feedback has not been compared yet with other strategies in the prevention of intra-dialytic hypotension. Moreover, the use of a preset post-dialytic plasma conductivity target in the "physiologic range"⁵⁴ (i.e. 14.0-14.2 mS/cm, roughly corresponding to a plasma sodium concentration of 138-140 mmol/l) might possibly lead to reduced sodium loading in patients with low pre-dialytic plasma sodium levels^{28,29,49}. The effect of conductivity controlled feedback, which is only

available on a single dialysis module (Diacontrol®), on sodium balance in comparison with other treatment strategies has also not been studied.

Another, more used, feedback method in the prevention of hemodynamic instability is blood-volume controlled feedback systems. Blood volume controlled feedback prevents a decline in blood volume below an individually set threshold by continuous adjustments of the ultrafiltration rate and dialysate conductivity in response to measured changes in relative blood volume. This threshold is based on an empirically determined relative blood volume below which the patient is known to develop complaints. Relative blood volume can be assessed during dialysis by measuring the change in hematocrit or protein content by optical methods or ultrasound⁵⁵.

The biofeedback system used in this thesis (Hemocontrol®; Hospal-Gambro, Mirandola, Italy) is based on a closed-loop automatic control system using three controlled variables and two control variables. These controlled variables are total weight loss, change in relative blood volume, and equivalent conductivity. Equivalent conductivity is a value which is defined as the mean dialysate conductivity value required to achieve the same sodium mass balance compared to standard hemodialysis with a fixed conductivity. The control variables consist of the ultrafiltration rate and the delivered dialysate conductivity. Discrepancies between ideal and achieved controlled variable values are processed by a multi-input/multi-output controller that in turn effectuates a response through the two actuators, the control variables ultrafiltration rate and dialysate conductivity. Changes in blood volume are determined by continuous relative blood volume monitoring. Total weight loss is measured volumetrically.

Although the mean dialysate conductivity is usually set at a “physiologic” level (14.0-14.2 mS/cm (~140-142 mmol/l)), the effect of these rapid fluctuations of dialysate conductivity on ionic removal has not yet been studied. Most studies, however, have not reported important changes in plasma sodium levels during biofeedback treatment. Blood volume controlled feedback, though shown to be effective in reducing intra-dialytic hypotension, has not been compared with other methods in the prevention of intra-dialytic hypotension. Also, the effect of blood volume controlled feedback on sodium balance has not been assessed in detail⁵⁶⁻⁵⁹.

The discussion above shows that many issues regarding sodium balance in hemodialysis therapy still remain unanswered.

2 Dialysis adequacy

Dialysis adequacy estimated by urea removal

The second part of the thesis focuses on the monitoring of dialysis adequacy.

Next to restoration of the water, electrolyte, and acid-base balance of the body, the removal of uremic toxins is the main goal of dialysis therapy. Although many uremic toxins are responsible for the uremic syndrome^{60,61} (only the removal of urea is used as a marker of dialysis adequacy, although urea per se does not appear to be highly toxic. However, urea removal indices were found to be related to outcome (ref. NCDS) and plasma urea is easy to measure, whereas the kinetic modelling of urea during dialysis is relatively straightforward⁶². Other relevant uremic toxins, such as phosphate or β -2 microglobulin, have different kinetics compared to urea⁶³.

Urea reduction ratio (URR)

The most simple method to express dialysis adequacy in terms of urea removal is the urea reduction ratio (URR), for which only pre- and post-dialytic plasma urea concentration is needed. It can be expressed as:

$$(1 - C_{\text{end}}/C_0) \times 100$$

C_{end} = urea concentration at the end of dialysis

C_0 = urea concentration at the start of dialysis.

URR is easy to calculate and is therefore widely used in clinical practice⁶⁴. However, a serious drawback of the use of URR resides in the fact that urea removal by ultrafiltration is not taken into account, nor the urea generation during dialysis. Thus, its application in individual therapy quantification introduces significant errors. It has been suggested that due to these limitations, the use of URR as index of dialysis dose might have a negative effect on treatment outcome and should not be used, although some studies showed a good correlation between URR and survival^{65,66,67}.

Neither European Best Practice Guidelines (EBPG) nor Kidney Disease Outcomes Quality Initiative (K-DOQI) advocate URR as an appropriate method for assessing dialysis adequacy^{68,69,70}. In the 2007 EBPG on dialysis strategies it has been suggested that URR should be used as an approximation for practical purposes, but not as a substitute for formal urea kinetic modelling⁶⁹.

Single pool Kt/V_{urea} (spKt/V)

spKt/V is the most commonly used marker to express dialysis dose, and its use is advocated by both K-DOQI and EBPG guidelines. Kt stands for dialyzer clearance (K) x dialysis time (t), which can be considered as the amount of blood which is cleared of urea during a dialysis treatment. V stands for the amount of urea distribution volume of the patient. Therefore, spKt/V is a dimensionless unit. With a spKt/V of 1.0, basically a volume of blood equal to the urea distribution volume has been totally

cleared of urea. With spKt/V , urea generation during dialysis, as well as urea removal during ultrafiltration is taken into account.

The following formula for spKt/V is advocated in K-DOQI guidelines⁷⁰:

$$\text{spKt/V} = -\text{LN}\left(\left(\frac{\text{C}_{\text{end}}}{\text{C}_0}\right) - 0.008 \cdot t\right) + \left(4 - 3.5 \cdot \left(\frac{\text{C}_{\text{end}}}{\text{C}_0}\right)\right) \cdot \frac{\text{Uf}}{\text{Wt}}$$

C_0 , C_{end} = urea concentration at start and end-session

Uf = ultrafiltration volume

Wt = post-dialytic body weight (kg)

t = treatment time in hours

With this formula, urea removal during dialysis is calculated according to single-pool kinetics. However, after dialysis, significant rebound of urea is observed, showing that urea kinetics do not follow a single pool model.

Which types of rebound can be distinguished?

There are three main causes of rebound after dialysis. The first type of rebound, occurring within 15–20 seconds after the end of dialysis is a result of access recirculation, if present. The effect of access recirculation can be circumvented by the methodology of post-dialytic blood sampling. The most used method is the “slow-flow” method, by which the speed of the dialyzer blood pump is reduced 15 seconds before the termination of dialysis. Immediate stopping of the blood pump may lead to ‘freezing’ of the blood sample and therefore to underestimation of the actual plasma urea concentration when access recirculation is present⁷⁰.

The second type of rebound is a result of cardiopulmonary recirculation, which takes place until 1–2 minutes after the end of dialysis. Cardiopulmonary recirculation occurs because a part of the purified blood, which returns to the heart, flows immediately back to the fistula without passing the tissues. Cardiopulmonary recirculation is inherently present in every haemodialysis treatment, except in patients with central venous catheters⁷¹. However, the effect of cardiopulmonary recirculation on urea rebound does not appear to be very large⁷². The effect of cardiopulmonary recirculation can be circumvented by taking the blood sample 3 minutes after the end of dialysis⁷⁰.

The third type of rebound, which appears to be a result of a disequilibrium of urea distribution within different body pools, and is lasting until 30–60 minutes after the end of dialysis, depending on the intensity of dialysis. It has been shown that 99% of the post-dialytic urea rebound was complete at 48 minutes and 94% at 30 minutes⁷³ after haemodialysis treatment. The cause of this phenomenon is still subject of debate and different hypotheses. A first hypothesis assumes that during dialysis, a concentration gradient exists between the intracellular and extracellular spaces,

because of resistance of the cell membrane to urea transport, which leads to rebound of urea from the intracellular space after the end of dialysis. A second hypothesis (regional flow model) assumes that this phenomenon is caused by the differences in perfusion of various tissues, which may lead to rebound of urea from the less well perfused regions of the body^{70,74,75}.

Equilibrated double pool Kt/V_{urea} (eKt/V)

The best way to compensate for rebound due to urea redistribution is to measure blood urea 30–60 minutes after the end of dialysis. Despite the fact that rebound may not be entirely complete, the eKt/V , which takes the 30-minutes post-dialytic sample into account, is often used in the literature as the reference method⁷⁶. However, this approach is cumbersome in clinical practice, both for hospital staff and patients. Therefore, several formulae have been developed in order to compensate for urea disequilibrium. One of the most frequently used formulae is the empirically derived Daugirdas–Schneditz formula, which corrects the single-pool Kt/V for treatment time⁷⁷. The derived values were found to be well related to the actual equilibrated Kt/V , and seem to be as reliable as values based on dialysate collection techniques⁷⁶.

The most commonly used formula for eKt/V , based on the regional blood flow two-pool urea kinetic model is:

$$eKt/V = \frac{spKt/V - (0.6 \times spKt/V)}{t} + 0.03$$

t = treatment time in hours

$spKt/V$ = singlepool Kt/V_{urea}

In general, also depending on the duration of dialysis, eKt/V is 0.15–0.20 lower than $spKt/V$.

In contrast to K-DOQI, the eKt/V is advocated by the EBP guidelines as the preferred tool to assess dialysis adequacy. Reasons for K-DOQI not to prescribe eKt/V as benchmark for dialysis adequacy are its mathematical relation to $spKt/V$, and the fact that shortened dialysis time (which increase the discrepancy between $spKt/V$ and eKt/V) are disallowed by K-DOQI guidelines. In general, K-DOQI did not consider the evidence for the use of eKt/V instead of $spKt/V$ of sufficient strength to justify the additional effort and target range⁷⁰.

As reaching the target levels of Kt/V_{urea} is associated with improved survival and decreased incidence and duration of hospitalization^{78,79}, the discussion whether URR, eKt/V or $spKt/V$ should be the preferred parameter in the assessment of dialysis adequacy remains.

Dialysis adequacy estimated from ionic dialysance

Current guidelines advocate to assess Kt/V_{urea} at least at a monthly basis. However, considerable variation in delivered dialysis dose has been observed between individual dialysis sessions⁸⁰. This would, given the relation between Kt/V_{urea} and clinical outcomes^{78,79} justify more frequent assessment of dialysis dose. However, for assessment of Kt/V by formal urea kinetic modelling pre- and post-dialysis blood sampling is needed, which makes more frequent assessment of Kt/V_{urea} by the standard approach, impractical. Therefore, reliable non-invasive assessment of dialysis dose would be a great asset for clinical practice.

An increasingly used method is the estimation of Kt/V_{urea} from ionic dialysance (Kt/V_{id}). As discussed in the previous section, ionic dialysance can be assessed during the dialysis session by temporarily increasing dialysate conductivity (~ equivalent to the dialysate sodium concentration) in the inlet port of the dialyzer and measuring the change in conductivity at the dialysate outlet^{81,86}. The effective ionic dialysance and the plasma conductivity of the patient are measured in an automated and non-invasive way. The underlying assumption is that plasma conductivity does not change during temporary changes in dialysate conductivity because of the large sodium distribution pool⁸², although this assumption has been questioned⁸³. Urea clearance can be assessed from ionic dialysance because sodium and urea have comparable molecular weights. This technique has already been integrated on some commercially available dialysis modules. Its great advantage would be the presence of an inexpensive, readily available on-line estimation of dialysis adequacy and sodium removal, which can be assessed at every dialysis treatment. In several studies, Kt/V_{id} appeared to be well related to Kt/V_{urea} ⁸⁴, although in some studies⁸⁵, an underestimation of Kt/V_{id} was observed as compared to Kt/V_{urea} . This was explained by the effects of cardiopulmonary recirculation, which would tend to overestimate “true” urea removal^{86,87,88}. Indeed, Mercadal et al. observed that after correction for recirculation, urea clearance and ionic dialysance were equivalent⁸⁸. Other authors⁸³ though attributed differences between ionic dialysance and urea removal to changes in the total body sodium pool due to the effect of conductivity pulses themselves. In addition, also the dialyser clearance and the charge of the dialysis membrane may influence the relation between ionic dialysance and urea clearance.

The influence of the estimation of urea distribution volume on Kt/V_{id}

Also the estimate of urea distribution volume deserves attention in the assessment of Kt/V_{id} . The ionic dialysance method only takes clearance and treatment time into account (Kt), whereas the V component has to be derived from anthropometric formulae or kinetic modelling. Nevertheless, several studies questioned the reliability of these anthropometry-based equations^{89,90}. In general, anthropometry-derived equations appear to underestimate the true urea distribution volume, which would partly offset the effect of underestimation urea clearance by ionic dialysance⁸⁶.

Assessment of V by urea kinetic modelling (V_{ukm}) may be more reliable than anthropometric derived V ⁹¹. Recently, an estimate of V which was calculated with the use of ionic dialysance measurements (V_{IOD}) themselves has been proposed (V_{IOD}), which correlated very well with V obtained by direct dialysis quantification and bio-impedance measurements^{92,93}. A comparison of V_{IOD} with other estimates of V regarding the agreement between Kt/V , assessed by eKt/V and Kt/V_{id} was only assessed in relatively small patient groups.

Appendix Mathematical definitions

1. Sodium balance: $V_{out} \times C_{out} - V_{in} \times C_{in}$
2. Sodium balance:
 = predialysis total body sodium–postdialysis total body sodium
 = predialysis plasma sodium x ((0.58 x target weight)+ultrafiltration volume)
 - postdialysis plasma sodium x (0.58 x target weight)
3. $PC = [Cd_{out} - (1 - D / Qd_{in}) \times Cd_{in}] / (D / Qd_{in})$
4. $D = (Qd_{in} + Qf) \times [1 - (Cd_{out1} - Cd_{out2}) / (Cd_{in1} - Cd_{in2})]$
5. $IMB = [(Qd_{out} \times Cd_{out}) - (Qd_{in} \times Cd_{in})] \times 10 \times \text{time (min)}$
6. $URR = (1 - C_{end}/C_0) \times 100$
7. $spKt/V = -\text{LN}\left(\left(\frac{C_{end}}{C_0}\right) - 0.008 \cdot t\right) + \left(4 - 3.5 \cdot \left(\frac{C_{end}}{C_0}\right)\right) \cdot \frac{Uf}{Wt}$
8. $eKt/V = \frac{spKt/V - (0.6 \times spKt/V)}{t} + 0.03$
9. V (Watson):
 males: $2,447 - 0,09516 \cdot A + 0,1074 \cdot Ht + 0,3362 \cdot Wt$
 females: $-2,097 + 0,1069 \cdot Ht + 0,2466 \cdot Wt$

V_{out} = volume of spent dialysate,
 C_{out} = concentration of solute in spent dialysate
 V_{in} = volume of fresh dialysate,
 C_{in} = concentration of solute in fresh dialysate
 PC = plasma conductivity
 Qf = ultrafiltration rate
 D = ionic dialysance
 Qd_{out} = dialysate flow at outlet
 Cd_{out} = dialysate conductivity at outlet
 Qd_{in} = dialysate flow at inlet
 Cd_{in} = dialysate conductivity at inlet
 C_0 = urea concentration at start session

C_{end} = urea concentration at end-session
U_f = ultrafiltration volume (in liters)
W_t = post-dialytic body weight (in kilograms)
H_t = length (in centimetres)
A = age (in years)
t = treatment time (in hours)
spKt/V = singlepool Kt/V
eKt/V = equilibrated, double pool Kt/V
URR = Urea Reduction Rate
V_{watson} = urea distribution volume calculated by the Watson formula
V_{iod} = urea distribution volume calculated by the ionic dialysance formula
V_{ukm} = urea distribution volume calculated by the urea kinetic modelling formula

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Chapter 2

Aim and outline of the thesis

Aim and outline of the thesis

The objective of this thesis is to study the added value in clinical practice of technological advances during hemodialysis by examining the influence of the following issues.

Variations in pre-dialytic plasma conductivity and the effect on ionic mass balance

In **Chapter 3** we describe how differences in dialysis sodium prescription affect diffusive ionic mass balance during a single dialysis session. Moreover, ionic mass balance by on-line conductivity measurements is validated against conductivity measurements in spent dialysate collections. In **Chapter 4** the long term variation in pre-dialytic plasma conductivity in hemodialysis patients treated with a fixed dialysate sodium concentration is addressed. In addition, the relation between variations in plasma conductivity and clinical parameters, such as inter-dialytic weight gain and blood pressure is studied. Furthermore, it is studied to which extent differences in pre-dialytic plasma conductivity result in differences in (diffusive) ionic mass balance. In this chapter, ionic mass balance is validated using sodium balance measurements by direct dialysate quantification. In **Chapter 5** the influence of sodium profiling as well as blood volume controlled feedback and conductivity controlled feedback on ionic mass balance is addressed. Additionally, the effects on hemodynamic stability of these different treatment modalities is studied. The effect of the imposed rapid fluctuations of dialysate conductivity during the assessment of plasma conductivity and ionic dialysance has not yet been studied. In **Chapter 6** the effect of ionic dialysance measurements on sodium load is assessed.

The different parameters for estimating dialysis adequacy and the effect on outcome

Chapter 7 studies the effects of treatment monitoring with different parameters of dialysis adequacy based on urea kinetic modelling, i.e. the urea reduction rate, eKt/V and $spKt/V$. This study was carried out in the NECOSAD cohort and addresses which percentage of patients would be classified as receiving an “adequate” or “inadequate” treatment dose based on target and minimally adequate levels of these different parameters. In addition also the prognostic significance of the different adequacy parameters will be discussed. In **Chapter 8** the agreement between Kt/V assessed by ionic dialysance and by formal urea kinetic modelling is assessed. Furthermore the effect of different estimates of urea distribution volume on dialysis adequacy on dialysis adequacy estimation is discussed. The mechanisms between the inter-treatment variability of Kt/V by ionic dialysance are also studied.

In **Chapter 9**, the results of the studies in the thesis are summarized and their implications are addressed.

Chapter 3

**Ionic mass balance and blood volume preservation
during a high, standard, and individualized dialysate
sodium concentration**

Karin EM Moret, Daxenos Hassell, Jeroen P Kooman, Frank van der Sande,
Paul GG Gerlag, A Warmold L van den Wall Bake, Jarno van den Bogaart,
Karel ML Leunissen

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Abstract

Background

Although a higher dialysate sodium concentration (DNa) is frequently used to improve hemodynamic stability during haemodialysis, few studies have compared ionic mass balance (IMB) during different DNa. Moreover, DNa is usually a standard prescription, whereas inter-individual pre-dialytic serum sodium levels may differ widely. The aims of the study were to assess IMB and the decline in blood volume (Δ BV) during isovolaemic HD as well as during HD combined with ultrafiltration (UF) during DNa [140], DNa [144], and an individualized DNa [ind], in which DNa is equal to pre-HD plasma conductivity $\times 10$.

Methods

IMB and plasma conductivity were assessed by on-line conductivity measurements (Diascan®; Hospal®) in 13 HD patients. After one hour of isovolaemic HD, measurements were continued during UF+HD until dry weight. Δ BV was assessed by an optical method (Hemoscan®).

Results

During isovolaemic HD with DNa [140] and [144], Pre-Na was significantly related to IMB ($r=0.83$ and $r=0.61$; $P<0.05$). Diffusive ionic mass influx from dialysate to patient occurred when the difference between DNa and pre-dialytic plasma sodium was larger than 5 mmol/l. During UF+HD, IMB was 318 ± 166 mmol during DNa [140], 277 ± 116 mmol during DNa [ind], and 239 ± 111 during DNa [144] (mean $\pm$ SD; $P<0.05$ compared with the other treatment modalities) whereas Δ BV did not differ significantly. In the five patients with a pre-dialytic sodium concentration below 140 mmol/l, ionic removal was significantly higher during DNa [ind] (324 ± 87) compared with DNa [140] (228 ± 127 mmol; $P<0.05$) without a significant difference in BV (-9.7 ± 1.6 vs $-7.8\pm2.3\%$).

Conclusion

A large difference in IMB was observed between DNa 144 and DNa 140, without a significant difference in Δ BV. In patients with low pre-dialytic serum sodium levels, diffusive ionic influx from the dialysate into the patient may occur. In patients with low pre-dialytic sodium levels, DNa [ind] leads to an enhanced ionic removal compared with DNa [140] without large differences in Δ BV.

Introduction

The dialysate sodium concentration is a two-edged sword. Whereas a low dialysate sodium concentration may lead to large removal of sodium but also to an impaired preservation of blood volume provoking intra-dialytic hypotension, a high dialysate sodium concentration may improve hemodynamic stability during dialysis, although possibly at the cost of increased inter-dialytic weight gain and hypertension. In general, an optimal dialysate sodium concentration would find a balance between both an adequate blood volume preservation and sodium removal¹. In earlier studies, but also more recently^{2,3}, several authors recommended higher dialysate sodium concentrations in order to prevent intra-dialytic hemodynamic instability in hypotension-prone dialysis patients^{2,3}. Few data are, however, available on ionic mass balance (IMB) during dialysis with different dialysate sodium concentrations, although such data are of pivotal importance in view of the relation between sodium, hypertension, and left ventricular abnormalities in dialysis patients⁴⁻⁶.

In most of the literature, the dialysate sodium concentration is seen as a standard prescription, whereas the pre-dialytic plasma sodium concentration may differ between dialysis patients. The fact that this phenomenon may lead to large inter-individual differences in diffusive ionic transfer suggests that individualization of dialysate, i.e. based on pre-dialytic plasma conductivity or sodium measurements or effected by biofeedback modules, would seem judicious. Nevertheless, although the use of individualization of the dialysate sodium concentration may be appealing in the sense of a more physiologic and patient-based dialysis prescription, it is not known whether such an approach actually improves the dialysis treatment in terms of the balance between blood volume preservation and ionic removal.

New techniques based on conductivity measurements enable the physician to assess IMB during dialysis, which is likely to be representative of sodium balance, due to the quantitative predominance of sodium ions in both plasma and dialysate. In this aspect, however, it is of great importance to distinguish between convective transport evoked by ultrafiltration and purely diffusive ionic transport. The aims of the present study were to first assess IMB *in vivo* both during isovolaemic dialysis as well as during haemodialysis combined with ultrafiltration using different dialysate sodium concentrations, and secondly to compare standard and individualized dialysate sodium concentrations in terms of blood volume preservation and IMB.

Subjects and methods

Study protocol

Validation study

During nine treatment sessions, IMB was assessed both by Diascan® (*vide infra*) and by direct dialysis quantification. Using direct dialysis quantification, the total amount of spent dialysate was collected in a box. Conductivity measurements were performed in a sample of spent dialysate taken from the box, as well as in a sample of incoming dialysate. IMB by direct dialysis quantification was assessed according to the formula:

$(Cd_{in} \times Qd \times \text{dialysis time}) - (Vd_{out} \times Cd_{out})$, in which

Qd is dialysate flow,

Cd_{in} is dialysate conductivity of incoming dialysate,

Vd_{out} is volume of spent dialysate, and

Cd_{out} is the conductivity of spent dialysate. Conductivity of incoming and spent dialysate was measured with a conductivity meter (IBP HDN-90, Hannover, Germany). Moreover, sodium concentration of incoming dialysate was assessed by ionometry (Vitros 950®; Johnson and Johnson).

Clinical study

Patients were studied during three dialysis sessions with dialysate sodium concentrations of, respectively, 140 mmol/l (14mS/cm) {DNa [140]}, and 144 mmol/l (14.4mS/cm) {DNa [144]}, and an individualized sodium concentration {DNa [ind]}. Dialysate sodium was individualized according to pre-dialytic plasma conductivity (dialysate sodium is equal to pre-dialytic plasma conductivity $\times 10$), as measured by Diascan® (Hospal®) (*vide infra*). Three different dialysis sessions with, respectively, DNa [140], DNa [144], and DNa [ind] were compared, in randomized order. Sessions were performed at exact intervals of one week, in order to prevent large differences in ultrafiltration volume and also to prevent an effect of a previous modification of dialysate sodium on the subsequent study sessions. In the other dialysis treatments, during which no measurements were performed, a dialysate sodium concentration of 140 mmol/l was used, as was standard policy in our clinic at the time of the investigation.

During each session, patients were first studied during one hour of isovolaemic dialysis, followed by combined ultrafiltration and haemodialysis until clinical dry weight, using the same dialysate sodium concentration. Parameters assessed were IMB, relative blood volume, serum sodium, and plasma conductivity, which were measured at the start of the study, after one hour of isovolaemic dialysis, and at the end of the dialysis session (after combined haemodialysis and ultrafiltration).

Patients

Thirteen patients were included in the study (eight male; five female). Mean $\pm$ SD age of the patients was 65.5 $\pm$ 16.0 years (range 26–81). Patients with acute renal insufficiency with severe hypotensive episodes were excluded. Mean dry body weight was 66.8 $\pm$ 12.2 kg (range 43–92). Seven patients still had residual renal function. Mean urine volume in the patient group was 770 $\pm$ 91 ml/day (range 0–2.25 l). All patients gave informed consent for participation in the study.

Dialysis schedule

The dialysis schedule of the patients was twice weekly in five patients and three times a week in eight patients. Mean treatment time was 231 $\pm$ 23 min (range 180–270). Polysulfone (F8HPS; Fresenius®) dialysis membranes were used. Composition of the dialysate was: potassium 2.0 mmol/l, calcium 1.5 mmol/l, magnesium 0.5 mmol/l, bicarbonate 32 mmol/l, acetate 3.0 mmol/l, and glucose 1 g/l. Temperature of the dialysate was 36°C. Patients were ultrafiltered until their clinically determined dry weight.

Study parameters

Ionic mass balance

IMB was estimated by Diascan® (Hospal®)^{7,8}. In short, Diascan® measures IMB by constant measurement of the conductivity in the dialysis outlet and inlet according to the formula:

$$\text{IMB} = [(Q_{d_{\text{out}}} \times C_{d_{\text{out}}}) - (Q_{d_{\text{in}}} \times C_{d_{\text{in}}})] \times 10 \times \text{time (min)}.$$

$Q_{d_{\text{out}}}$ and $Q_{d_{\text{in}}}$ are dialysate flow at, respectively, outlet and inlet; $C_{d_{\text{out}}}$ and $C_{d_{\text{in}}}$ are dialysate conductivity at, respectively, outlet and inlet. A positive IMB means sodium removal from the patient, a negative IMB means sodium transport to the patient.

Plasma conductivity

Plasma conductivity (P_c) is measured by Diascan® by measuring dialysance (D) in combination with measurements of $C_{d_{\text{out}}}$ and $C_{d_{\text{in}}}$ according to the formula:

$$P_c = [C_{d_{\text{out}}} - (1 - D/Q_{d_{\text{in}}}) \times C_{d_{\text{in}}}] / (D/Q_{d_{\text{in}}}).$$

D is assessed every 30 min by measuring the increase in $C_{d_{\text{out}}}$ after a temporary increase in $C_{d_{\text{in}}}$ by 1 ms/cm according to the formula:

$$D = (Q_{d_{\text{in}}} + Q_f) \times [1 - (C_{d_{\text{out}1}} - C_{d_{\text{out}2}) / (C_{d_{\text{in}1}} - C_{d_{\text{in}2}})],$$

where 1 and 2 indicate, the measurements before and after the temporary increase in $C_{d_{\text{in}}}$ ^{7,8} respectively, $Q_{d_{\text{in}}}$ is dialysate flow at inlet and Q_f is ultrafiltration rate.

Relative blood volume

Blood volume was measured continuously by continuous optical assessment of changes in hemoglobin during the dialysis session (Hemoscan®)⁹.

Serum sodium

Serum sodium was assessed by ionometry (Vitros 950®), which assesses sodium activity in the serum. Sodium activity is automatically converted to the molar ionized sodium concentration. Obtained values were corrected by converting the molar concentration to flame photometer values by a standard correction factor (0.93)¹⁰. The coefficient of variation for this method, as given by the manufacturer, is 0.4%.

Statistical analysis

Results obtained at the different treatment sessions were compared using Friedman's ANOVA and, if significant, further analysed by a Wilcoxon test. Correlations between variables were assessed by Pearson's r . P values <0.05 were considered significant. Statistical analysis was performed using a SPSS 10.0 software package.

Results

Validation study

IMB assessed by Diascan® and direct dialysis quantification were highly significantly related ($r=0.94$; $P<0.05$; Figure 3.1). Dialysate conductivity of incoming dialysate assessed by the Integra® monitor was highly significantly related to dialysate conductivity assessed by the independent method ($r=0.99$; $P<0.05$). Moreover, dialysate sodium concentration and dialysate conductivity were highly significantly related ($r=0.96$; $P<0.05$).

Isovolaemic dialysis

All measurements were successful, except for one initial plasma conductivity measurement during DNa [140]. Pre-dialytic plasma conductivity and serum sodium concentrations are displayed in Tables 3.1 and 3.2. Pre-dialytic plasma conductivity was significantly related to pre-dialytic serum sodium ($r=0.80$; $P<0.05$).

Figure 3.1 Relation between IMB assessed by dialysate collection and Diascan®.

Table 3.1 Plasma conductivity and ionic mass balance during isovolaemic dialysis, followed by haemodialysis combined with ultrafiltration.

	Plasma conductivity (ms/cm)			IMB (mmol)	
	A	B	C	B	C
DNa[140]	14.21±0.31	14.18±0.22	14.11±0.16	33.6±31.5*	317.7±166.0
DNa[144]	14.26±0.20	14.26±0.16	14.32±0.10 [#]	11.3±26.0	238.7±116.4*
DNa[ind]	14.24±0.22	14.22±0.21	14.24±0.24	24.8±21.7	276.9±116.2

* $P < 0.05$ compared with DNa[140] and DNa[ind]; [#] $P < 0.05$ compared with pre-HD. Values as mean ± SD. IMB, ionic mass balance; A, start dialysis; B, end isovolaemic dialysis ($t = 1$ h); C, end dialysis combined with ultrafiltration. NB: a more positive IMB corresponds to a larger ionic removal.

Table 3.2 Serum sodium, decline in blood volume, and ultrafiltration volume during isovolaemic dialysis followed by haemodialysis combined with ultrafiltration.

	Serum sodium (mmol/l)			BV (%)		UF-vol (l)
	A	B	C	B	C	
DNa[140]	139.1±2.0	139.5±2.8	139.4±1.3	-1.8±1.3	-8.6±4.6	1.5±1.0
DNa[144]	139.2±1.9	138.6±2.5	140.2±1.5 [#]	-1.5±1.3	-7.4±3.7	1.4±0.9
DNa[ind]	140.0±2.1	140.1±2.1	140.3±2.0	-1.9±1.3	-8.4±2.2	1.4±0.73

Plasma conductivity and plasma sodium did not change significantly during isovolaemic dialysis (Tables 3.1 and 3.2). Although precision of the measurements was not formerly tested in this study, we got an impression on the precision. Plasma sodium levels at the start and after the end of isovolaemic dialysis were correlated, as were plasma conductivity measurements. The correlation coefficient was $r = 0.92$ for

plasma conductivity but only $r=0.70$ for plasma sodium levels ($P<0.015$), suggesting, but not proving, a higher precision of plasma conductivity measurements. Mean dialysate conductivity during DNA [ind] was 143 ± 2.1 mmol/l. IMB differed significantly between the session with DNA [144] on the one hand and DNA [140] and DNA [ind] on the other, whereas DNA [140] and DNA [ind] were not significantly different (Table 3.1). IMB during isovolaemic dialysis with DNA [144] and DNA [140] was significantly related to the pre-dialytic plasma conductivity ($r=0.97$ and $r=0.81$; $P<0.05$) (Figures 3.2A and 3.3A), and to a somewhat lesser degree, to the pre-dialytic serum sodium concentration ($r=0.83$ and $r=0.61$; $P<0.05$) (Figures 3.2B and 3.3B). A negative IMB, indicating net ionic influx from dialysate to patient, occurred when the pre-dialytic serum sodium concentration was more than 5 mmol/l below the dialysate sodium concentration (Figures 3.2B and 3.3B). The relative blood volume declined slightly during all treatment sessions without significant differences between the sessions (Table 3.1). There was no significant relation between the change in blood volume and IMB during isovolaemic dialysis with either treatment session.

Figure 3.2 (A) Relation between pre-dialytic plasma conductivity and IMB during isovolaemic dialysis (HD) with a dialysate sodium concentration of 140 mmol/l (DNA [140]). (B) Relation between pre-dialytic serum sodium and IMB during isovolaemic dialysis (HD) with a dialysate sodium concentration of 140 mmol/l (DNA [140]).

Ultrafiltration combined with haemodialysis

The mean ultrafiltration volume was comparable between the three treatment sessions (Table 3.2).

Serum sodium increased significantly during DNA [144] but not during the other treatment modalities (Table 3.2). Moreover, IMB was significantly less positive during DNA [144], indicating less ionic removal, compared with DNA [140] and DNA [ind] ($P<0.05$) (Table 3.2 and Figure 3.4). IMB was significantly related to ultrafiltration volume during both DNA [140] ($r=0.87$), DNA [144] ($r=0.81$), and DNA [ind] ($r=0.64$; all

$P<0.05$). During DNa [140], but not during the other treatment sessions, IMB was significantly related to pre-dialytic plasma conductivity ($r=0.59$; $P<0.05$).

Figure 3.3 (A) Relation between pre-dialytic plasma conductivity and IMB during isovolaemic dialysis (HD) with a dialysate sodium concentration of 144 mmol/l (DNa [144]). (B) Relation between pre-dialytic serum sodium and IMB during isovolemic dialysis (HD) with a dialysate sodium concentration of 144 mmol/l (DNa [144]).

Figure 3.4 IMB during ultrafiltration combined with haemodialysis (UF+HD) with different dialysate sodium concentrations. DNa [140], dialysate sodium 140 mmol/l; DNa [144], dialysate sodium 144 mmol/l; DNa [ind], individualized dialysate sodium. Box indicates the 25th–75th percentile range (line in box, median). Capped bars indicate the 10th–90th percentile range.

The decline in relative blood volume (Table 3.2 and Figure 3.5) did not differ between the three treatment sessions. However, daily inter-dialytic weight gain following the treatment session was significantly higher after DNa [144] (0.66 ± 0.33 kg/day) compared with DNa [140] (0.57 ± 0.33 kg/day; $P < 0.05$), whereas the difference with DNa [ind] (0.58 ± 0.30) did not reach significance.

Figure 3.5 Decline in blood volume (BV) during ultrafiltration combined with haemodialysis (UF+HD) with different dialysate sodium concentrations. DNa [140], dialysate sodium 140 mmol/l; DNa [144], dialysate sodium 144 mmol/l; DNa [ind], individualized dialysate sodium. Box indicates the 25th–75th percentile range (line in box, median). Capped bars indicate the 10th–90th percentile range.

The change in systolic blood pressure during the entire dialysis session (which was 12.7 ± 21.0 mmHg during DNa [140], 0.0 ± 15.3 mmHg during DNa [144], and 5.9 ± 17.4 mmHg during DNa [ind]) did not differ significantly between the different dialysis sessions, although it tended to be higher during DNa [140] compared with DNa [ind] ($P = 0.08$). Also, the decline in diastolic blood pressure (which was -5.6 ± 12.6 mmHg during DNa [140], -7.5 ± 14 mmHg during DNa [144], and -2.4 ± 9.4 mmHg during DNa [ind]) did not differ significantly between the different dialysis sessions.

When patients with a pre-dialytic serum sodium concentration below 140 mmol/l or higher or equal to 140 mmol/l were analysed separately ($n = 5$), IMB was significantly higher during DNa [ind] compared with DNa [140] in patients with a pre-dialytic serum sodium concentration below 140 mmol/l (Figure 3.6) (324 ± 87 vs 228 ± 127 mmol; $P < 0.05$) whereas the decline in relative blood volume did not differ significantly (-9.8 ± 1.6 vs $-7.8 \pm 2.3\%$; $P = \text{NS}$). In contrast, in patients with a pre-dialytic serum sodium

concentration higher or equal to 140 mmol/l ($n=8$), IMB was significantly lower during DNa [ind] compared with DNa [140] (254 ± 123 vs 350 ± 178 mmol; $P < 0.05$) (Figure 3.5) whereas also in these patients, the decline in relative blood volume did not differ significantly (-7.1 ± 1.8 vs $-8.1 \pm 3.11\%$).

Figure 3.6 IMB during ultrafiltration combined with haemodialysis during dialysis with dialysate sodium concentrations of 140 mmol/l (DNa [140]) and individualized dialysate sodium (DNa [ind]) in patients with a pre-dialytic serum sodium concentration <140 (left) and ≥ 140 mmol/l (right). Box indicates the 25th–75th percentile range (line in box, median). Capped bars indicate the 10th–90th percentile range.

Discussion

The main findings of the present study are first, the large difference in ionic mass balance between haemodialysis with DNa [140] and DNa [ind] on the one hand and DNa [144] on the other, in combination with the small and non-significant difference in blood volume preservation between these modalities; secondly, the strong relation between pre-dialytic plasma sodium and plasma conductivity with ionic mass balance, which explains the diffusive ionic influx during isovolaemic dialysis in patients with low pre-dialytic plasma sodium levels; thirdly, the increased ionic removal during DNa [ind] in patients with low pre-dialytic plasma sodium levels and reduced ionic removal in patients with high pre-dialytic plasma sodium levels despite the absence of differences in blood volume preservation compared with DNa [140].

Ionic mass balance measurements by Diascan® appears to be suitable in detecting ionic changes during dialysis, as shown by the good agreement between Diascan® measurements and conductivity measurements in spent dialysate obtained during an entire dialysis session. As a result of the abundance of sodium ions in both dialysate and plasma, it is likely that IMB reflects predominately sodium balance during dialysis. It should, however, be mentioned that due to rapid changes in pH, chloride, and

bicarbonate, the relation of conductivity measurements to sodium balance may deviate slightly during dialysis. Moreover, in the present study, the relation between both plasma sodium and plasma conductivity levels was not completely linear. We believe, however, that this phenomenon might be due to a lack of precision of sodium measurements, as shown by the greater reproducibility of plasma conductivity measurements compared with plasma sodium levels, presented in the results section on isovolaemic dialysis. Moreover, the relation between pre-dialytic plasma conductivity measurements and IMB in the present study was far stronger than that obtained using plasma sodium measurements. The possible lack of preciseness of plasma sodium determination raises some doubt on the usefulness of monitoring plasma sodium levels in order to detect differences in ionic removal between various treatment modalities¹¹.

Both during isovolaemic dialysis, as well as during haemodialysis combined with ultrafiltration, a significant difference in ionic mass balance was observed between DNa [144] compared with DNa [140] and DNa [ind], indicating less ionic removal during DNa [144]. Moreover, plasma sodium levels increased significantly during DNa [144], but not during the other treatment modalities. The mean difference in measured ionic mass balance between high and standard sodium dialysate was approximately 90 mmol during an entire dialysis session, in theory corresponding to 2000 mg of sodium, thus the entire recommended daily sodium intake of a dialysis patient. The long-term clinical significance of this phenomenon cannot be elucidated from the present study but may not be negligible in view of the strong arguments for a relation between sodium, hypertension, and cardiac abnormalities in dialysis patients^{4,5}. Indeed, even inter-dialytic weight gain was higher after treatment with DNa [144]. However, only three single treatments were compared in this study and effects of different dialysate sodium prescription on ionic mass balance need to be repeated in more long term studies. Remarkable was the small and non-significant difference in blood volume preservation between the three treatment modalities. Nevertheless, in this stable group of dialysis patients, the decline in systolic blood pressure tended to be somewhat higher during DNa [140] compared with DNa [144]. The net diffusive ionic influx during DNa [140] in patients with low pre-dialytic plasma sodium levels is a phenomenon not often described in the literature, but is in line with earlier experimental data and theoretical considerations¹¹⁻¹³. In the present study, diffusive ionic influx was observed when the plasma sodium concentration was approximately 2 mmol/l lower than the dialysate sodium concentration. Factors influencing diffusion between dialysate and plasma are complex and include the sodium concentration in plasma water, the Donnan effect, and the formation of complexes of sodium ions with anions in plasma water and dialysate¹¹⁻¹³, as described in the Introduction.

Individualization of the dialysate in the present study was achieved by adjusting dialysate conductivity (which corresponds to DNa^7) to the pre-dialytic plasma conductivity of the patient. This approach was performed because (effective) plasma

conductivity measured by Diascan® is only related to the concentration of sodium ions which are free to diffuse and not trapped by the Donnan effect⁷. Individualization of DNa appeared predominantly relevant in patients with low pre-dialytic sodium levels, because in these patients, an increased ionic removal was achieved compared with DNa [140] whereas the decline in blood volume did not differ significantly. Nevertheless, the mean observed difference of approximately 2% might again be relevant in some patients. Therefore, it would certainly seem judicious to apply blood volume measurements if individualization of DNa is to be applied in hypotensive-prone dialysis patients with low pre-dialytic plasma sodium levels.

In the patients with higher pre-dialytic sodium levels, ionic removal was actually less during DNa [140] compared with DNa [ind] whereas again the decline in blood volume was not apparently different from DNa [140].

Drawbacks of the study are first the relatively small number of included patients, although this does not appear to have influenced the primary goal of the study, i.e. to assess IMB during different dialysate [Na] concentrations. Moreover, because the main objection was to study IMB and blood volume preservation during different dialysate sodium concentrations, stable haemodialysis patients were included. Further studies should also address the feasibility of individualized sodium concentrations of the dialysate in hypotension-prone dialysis patients.

Moreover, several patients still have residual renal function, which might have interfered with the influence of dialysate sodium prescription on inter-dialytic weight gain.

In conclusion, comparing three single sessions differing in dialysate sodium concentration, a relatively large difference in IMB, which may amount to the entire recommended daily sodium intake of a dialysis patient, was observed between DNa [144] on the one hand and DNa [140] and DNa [ind] on the other despite a nearly comparable blood volume preservation. In patients with a low pre-dialytic plasma sodium concentration, net diffusive ionic influx from the dialysate to the patient may occur during a fixed DNa. In patients with a low pre-dialytic plasma sodium concentration, individualization of dialysate sodium led to an improved ionic removal in patients, apparently without large implications for blood volume preservation during dialysis.

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Chapter 4

Variations in pre-dialytic plasma conductivity in dialysis patients: effect on ionic mass balance, blood pressure and interdialytic weight gain

Karin Moret, Charles Beerenhout, Jeroen Kooman

ASAIO in press

Abstract

Background

In this study, variations in plasma conductivity (PC), as a surrogate marker of plasma sodium, as well as its relation with intra-dialytic ionic mass balance (IMB) and blood pressure were assessed in 73 patients. PC and IMB were retrieved on a treatment-to-treatment basis during a 6-months period. Dialysate sodium was 140 mmol/l. 4070 treatments were analyzed.

Methods and Results

Mean coefficient of variation for pre-dialytic PC was 1.3%, and mean intra-individual range in pre-dialytic PC measurements during the six months follow-up period was 0.9 mS/cm [$\sim$ plasma sodium 9 mmol/l]. Pre-dialytic PC was related to both diffusive and total IMB ($r=0.91$; $P<0.001$ and $r=0.35$; $P<0.01$). The average diffusive IMB over a six-month period was negative in 33% of patients, and the average PC increased during dialysis in 14% of patients. Averaged pre-dialytic PC was significantly related to systolic blood pressure ($r=0.35$; $P<0.01$), whereas within patients, pre-dialytic systolic blood pressure was significantly different between treatments with the lowest and highest pre-dialytic PC (139 ± 24 versus 147 ± 21 mmHg; $P<0.05$).

Conclusion

Concluding, depending on PC, diffusive ionic transfer from dialysate to patient may occur in a significant percentage of patients using a dialysate sodium concentration of 140 mmol/l. Variations in PC are related to blood pressure, which might suggest a volume-independent effect of sodium.

Introduction

Volume and sodium overload in dialysis patients are related to hypertension, edema and left ventricular dilatation¹. Preliminary data suggest that, apart from volume, sodium might also have an independent effect on blood pressure regulation in dialysis patients^{2,3}.

During dialysis, the main determinant of sodium removal during dialysis is the ultrafiltration volume (convective mass transfer). However, also the contribution of diffusive mass transfer of sodium may be significant⁴. As such, the prescription of the dialysate sodium concentration has an important effect on sodium balance during dialysis. With the advent of dialysate conductivity monitoring, it has become possible to approximate sodium fluxes during dialysis by means of the assessment of intra-dialytic ionic mass balance (IMB), as well as plasma conductivity (PC) as a surrogate of plasma sodium⁴⁻⁸. These developments offer the opportunity to study sodium balance in more detail. The main advantage of PC is, that it can be used on a treatment-to-treatment basis without need for blood sampling.

Whereas previous studies have focused on the effect of modifications of dialysis treatment, such as sodium profiling^{4,5,9,10} in relatively small groups of patients, little is known about sodium balance on a treatment to treatment basis during dialysis with standard sodium concentrations (e.g. 140 mmol/l) at facility level. One study showed an increase in plasma sodium during dialysis in a significant subset of patients with the use of a dialysate sodium concentration of 140 mmol/l¹¹. Pre-dialytic plasma sodium levels are generally considered to be stable in dialysis patients, assuming a fixed sodium set-point in dialysis patients^{12,13}, which may be of importance when dialysate sodium prescriptions are individualized. However, long term studies on sodium balance and variations in plasma sodium are scarce.

The aim of the present study was to assess variations in PC, as a surrogate marker of plasma sodium on a treatment to treatment basis at facility level. Moreover, the relation of inter and intra-individual changes in PC with IMB, blood pressure, relative blood volume (RBV) and inter-dialytic weight gain was assessed.

Methods

Study protocol

In the dialysis centre of Maxima Medical Centre Veldhoven, The Netherlands, treatment data on PC, IMB, and changes in RBV are automatically stored in a database on a treatment to treatment basis. Data were retrieved from this database for a consecutive period of 6 months in each patient, and were randomly collected in the period between august 2006 and November 2007. Moreover, in this database, pre- and post-dialytic BP and body weight are recorded. The study was carried out

according to the declaration of Helsinki and approved by the local institutional review board.

Data from 73 chronic dialysis patients were recorded. Patient characteristics are displayed in Table 4.1. All patients were on thrice-weekly hemodialysis, except for two patients, who were treated with twice-weekly dialysis sessions. All patients were treated with Integra® (Hospal-Gambro, Mirandola, Italy) device, by which PC, IMB and changes in relative blood volume are automatically assessed and recorded. Polysulfone, low flux dialysis membranes (F8HPS®, Fresenius, Bad Homburg, Germany) were used. At the time of the study, prescription of the dialysate was: sodium 140 mmol/l (conductivity 14.0 mS/cm), potassium 2.0 mmol/l, calcium 1.5 mmol/l, magnesium 0.5 mmol/l, bicarbonate 32 mmol/l, acetate 3.0 mmol/l and glucose 1 g/l. Setting of the dialysate conductivity of the dialysis machine was 14mS/cm. Temperature of the dialysate was 36°C. Patients were ultrafiltrated until their clinically determined dry weight. Fifteen patients were treated with the Hemocontrol® (Hospal-Gambro) biofeedback module, for which also an equivalent dialysate conductivity of 14.0 mS/cm was prescribed.

Table 4.1 Patient characteristics.

Age (years)	67 ± 16
Male/Female	42 / 31
Dry weight (kg)	70.2 ± 14
Dialysis duration (hours)	3.9 ± 0.38
Dialysis frequency (per week)	2.9 ± 0.3
Residual Glomerular filtration rate (ml/min)	1.1 ± 1.8

Ionic mass balance

Intra-dialytic IMB was estimated by Diascan® (Hospal-Gambro) integrated in the Integra® dialysis module^{8,14}. In short, Diascan® measures IMB by constant measurement of the conductivity in the dialysis outlet (Cd_{out}) and inlet (Cd_{in}). IMB is reported directly by the dialysis module. By convention, and also as such reported by the Integra® device, a positive IMB reflects net ionic removal from the patient, a negative IMB means net ionic transfer from dialysate to the patient⁶. Diffusive IMB was assessed by the following formula:

$$\text{diffusive IMB} = \text{total IMB} - [(\text{mean PC} \times 10.4) - 9.57] \times \text{UF volume}^6.$$

Validation of IMB measurements

In 22 patients, direct dialysis quantification by Quantiscan® was performed during a single dialysis session. Quantiscan® continuously samples a small amount of the spent dialysis fluid. Electrolytes were assessed in duplicate in the spent dialysis fluid: sodium

(flame photometry and indirect ionometry), potassium, calcium, phosphate, bicarbonate and chloride. Sodium balance was assessed as follows:

$$[C_{out} \times V_{out}] - [C_{in} \times V_{in}]$$

C_{out} and C_{in} are the sodium concentration in spent and fresh dialysate, respectively. V_{out} and V_{in} are the volume of spent and incoming dialysate.

V_{out} is calculated as (dialysate flow rate (ml/min) + ultrafiltration rate (ml/min)) x dialysis time (min)

and V_{in} as dialysate flow rate (ml/min) x dialysis time (min). The same procedure was followed for the other ions.

Plasma conductivity

PC was measured and reported directly by Diascan® by measuring dialysance (D) in combination with measurements of Cd_{out} and Cd_{in} according to the formula:

$$PC = [Cd_{out} - (1 - D/Qd_{in}) \times Cd_{in}] / (D/Qd_{in})$$

D is assessed every 30 min by measuring the increase in Cd_{out} after a temporary increase in Cd_{in} by 1 mS/cm according to the formula:

$$D = Qd_{in} + Qf \times [1 - (Cd_{out1} - Cd_{out2}) / (Cd_{in1} - Cd_{in2})]$$

1 and 2 indicate, respectively, the measurements before and after the temporary increase in Cd_{in} ^{4,14}, Qd_{in} = dialysate flow at inlet, Qf = ultrafiltration rate

Plasma sodium

Plasma sodium levels were assessed before dialysis, approximately once monthly, by indirect ionometry (Vitros 950®). Plasma sodium levels were available in 332 treatments. The relation between PC and plasma sodium given in the literature is:

$$\text{Plasma sodium} = (PC \times 10.4) - 9.57^{6,7}.$$

Relative blood volume, blood pressure and residual GFR

Changes in relative blood volume were measured continuously by continuous optical assessment of changes in haemoglobin during the dialysis session (Hemoscan®, Hospal-Gambro). Blood pressure was taken as part of the clinical routine in sitting position just prior to the start of dialysis treatment. Body weight was measured, as part of the clinical routine, on a gravimetric scale. Residual GFR was assessed by inter-dialytic urine collections as the mean of urea and creatinine clearance.

Data analysis

Intra- and inter-individual variations in PC are reported by means of the range, standard deviation, and coefficient of variation. The relation between pre-dialytic PC, IMB, relative blood volume, interdialytic weight gain and blood pressure was assessed by correlation analysis (Pearson's r). Measurements during the 6 months period were

also pooled for each patient, and the mean of these data was used for analysis. Multiregression analysis was used where necessary. Regarding intra-individual variations, pre-dialytic blood pressure and interdialytic weight gain were compared between the session with the highest and lowest value of PC and analyzed using a paired student-t test. Correction for ultrafiltration volume and timing of the dialysis shift (after longest or short dialysis interval) was performed using univariate analysis with lowest or highest plasma conductivity as fixed factor and timing of dialysis shift and ultrafiltration volume as covariates.

Results

In total, 4070 measurements were retrieved in 73 patients. The mean number of treatment analysed was 56 [range 45 to 63 treatments]. Missing data were amongst others, the result of technical problems with the data management tool. The mean of the pooled data collected during the 6 months period for the patient is summarized in Table 4.2, separately presented for patients on Hemocontrol and standard dialysis treatment.

Table 4.2 Summary of parameters (6 months data pooled for each patient).

	Standard dialysis (n=58)	Hemocontrol (n=15)
Pre-dialytic PC (mS/cm)	14.19 ± 0.22	14.39 ± 0.14
Post-dialytic PC (mS/cm)	14.06 ± 0.09	14.07 ± 0.06
Total IMB (mmol/treatment)	342.8 ± 140.8	463.8 ± 57.6
Diffusive IMB (mmol/treatment)	26.8 ± 64.5	95.6 ± 35.8
Inter-dialytic weight gain (kg)	2.5 ± 1.0	2.7 ± 0.5
Decline in relative blood volume (%)	-7.9 ± 2.7	-7.9 ± 2.3
Pre-dialytic systolic BP (mmHg)	143.2 ± 18.4	153.2 ± 15.3
Pre-dialytic diastolic BP (mmHg)	78.6 ± 11.3	81.0 ± 0.9
% patients with negative IMB	32.9	0
% patients with increasing PC	13.7	0

PC=plasma conductivity (mS/cm); IMB=ionic mass balance (mmol/treatment); BP=blood pressure (mmHg)

Diffusive mass balance was 18.3±16.7% of convective mass balance. Whereas total IMB was positive (indicating net ionic transfer from the patient to the dialysate) in all patients using the pooled data, the averaged diffusive IMB was negative (indicating diffusive ionic transfer from dialysate to patient) in 33% of patients. In 14% of patients, the averaged PC increased during dialysis. As shown in Table 4.3, the only parameter which distinguished between patients with respective negative or positive diffusive IMB, or an increase or decrease in PC during dialysis, was the pre-dialytic PC. For intra-individual variations in pre-dialytic PC, the coefficient of variation during the 6 months follow-up period was 1.3%. For post-dialytic PC, the coefficient of variation was 1.0%. The mean (14.31±0.19 versus 14.21±0.23) and coefficient of variation [1.2

vs 1.3%] of pre-dialytic PC was not significantly different between patients with (n=15) or without diabetes mellitus (n=58)

Table 4.3 Differences between patients with a (mean averaged) negative of positive diffusive IMB and increase or decrease in PC during dialysis.

	IMB<0	IMB≥0		PC ↑	PC ↓	
	Mean±SD	Mean±SD	P value	Mean±SD	Mean±SD	P value
	24	49		10	63	
Age	70.7±13.6	66.7±16.9	NS	69.0±15.5	67.1±16.2	NS
Diabetes Mellitus	n=4 (17%)	n=11 (22%)	NS	n=0	n=15 (24%)	0.08
Pre-dialytic PC (mS/cm)	14.00±0.18	14.34±0.14	<0.001	13.83±0.11	14.29±0.15	<0.001*
Inter-dialytic weight gain (kg)	2.6±1.0	2.5±0.8	NS	2.8±1.0	2.5±0.9	NS

Mean values (SD) are presented for continues variables. Significant, $P<0.05$.

IMB<0 means net diffusive ionic transport from dialysate to patient. PC=plasma conductivity (mS/cm); IMB=ionic mass balance (mmol/treatment).

Within patients, pre-dialytic PC was $13.78 \text{ mS/cm} \pm 0.29$ before the treatment with the lowest pre-dialytic PC and $14.65 \text{ mS/cm} \pm 0.25$ before the treatment in which the highest pre-dialytic PC was recorded. The intra- and inter-patient variations in pre-dialytic PC can also be observed in Figure 4.1A and 4.1B. The variation in the CV of pre-dialytic PC is shown in Figure 4.1C.

Although the observation period was not designed to assess seasonal variations in detail, we observed a significantly difference between the various seasons with the lowest values in autumn ($14.21 \pm 0.28 \text{ mS/cm}$), followed by summer ($14.22 \pm 0.28 \text{ mS/cm}$), winter (14.25 ± 0.30) and spring ($14.27 \pm 0.28 \text{ mS/cm}$) ($p<0.001$). Regarding the timing of the dialysis shift, we also compared pre-dialytic PC between treatments after the longest shift, and the other treatments. No significant difference in PC was observed: 14.24 ± 0.29 before the longest shifts and 14.25 ± 0.29 before the other shifts. The variation in post-dialytic PC was less as compared to pre-dialytic PC . Mean SD for post-dialytic PC was 0.09 mS/cm . Post-dialytic PC was $13.85 \text{ mS/cm} \pm 0.19$ after the treatment with the lowest pre-dialytic PC and $14.30 \text{ mS/cm} \pm 0.20$ after the treatment in which the highest pre-dialytic PC was recorded (Table 4.4).

Figure 4.1A Inter and intra-dialytic variation in pre-dialytic plasma conductivity (mean $\pm$ SD). The horizontal line depicts a PC of 14.0 mS/cm. PC=plasma conductivity (mS/cm)

Figure 4.1B Inter and intra-dialytic variation in post-dialytic plasma conductivity (mean $\pm$ SD). The horizontal line depicts a PC of 14.0 mS/cm. PC=plasma conductivity (mS/cm)

Figure 4.1C Coefficient of variation for plasma conductivity: frequency and distribution in patients
PC=plasma conductivity (mS/cm)

Relation between PC, IMB and hemodynamic parameters

In the 4070 measurements, pre-dialytic PC was significantly related to diffusive IMB ($r=0.82$; $P<0.001$) (Figure 4.2). The same held true for diabetic patients ($n=15$), which were analyzed in a subgroup ($r=0.86$; $P<0.001$). Total and diffusive IMB, as well as inter-dialytic weight gain were not significantly different between patients with or without diabetes mellitus.

The mean averaged PC during the 6 months period in the 73 patients was significantly related to total ($r=0.37$; $P<0.01$) and diffusive IMB ($r=0.91$; $P<0.001$), as well as to the change in PC during dialysis ($r=-0.85$; $P<0.001$). Total IMB was strongly related to ultrafiltration volume ($r=0.88$). Pre-dialytic PC was significantly related to pre-dialytic systolic blood pressure ($r=0.35$; $P<0.01$) [Figure 4.3A], but not to diastolic blood pressure ($r=0.1$; $P=NS$) or interdialytic weight gain in the period before ($r=-0.09$; $P=NS$). Using multiregression analysis, the relation between pre-dialytic systolic BP and pre-dialytic PC ($\beta=0.37$; $P=0.002$) was independent of inter-dialytic weight gain, and the number of antihypertensive agents used ($\beta=0.14$; $P=NS$). Although the relation between pre-dialytic PC and diffusive IMB was comparable ($r=0.84$; $P<0.001$) in the subgroup of patients on Hemocontrol®, diffusive IMB was positive in all patients whereas no rise in PC was observed.

Figure 4.2 Relation between pre-dialytic PC and diffusive IMB
PC=plasma conductivity (mS/cm);
IMB=ionic mass balance (mmol/treatment)

Intra-patient variations in pre-dialytic PC

When analyzing the effect of intra-patient variations of PC, significant differences in IMB, pre-dialytic systolic (Figure 4.3B) and diastolic blood pressure were observed between the treatments with the lowest and highest pre-dialytic PC, whereas interdialytic weight gain (in the period before the highest and lowest PC) were not significantly different (Table 4.4). There was no significant relation between the absolute difference in blood pressure and the corresponding difference in PC between both treatments.

Table 4.4 Intra-patient differences between treatments with the highest and lowest pre-dialytic PC.

	<i>Lowest PC</i>	<i>Highest PC</i>	
Pre-dialytic PC (mS/cm)	13.78±0.29	14.65±0.25	<0.001
Post-dialytic PC (mS/cm)	13.85±0.19	14.30±0.20	<0.001
Total IMB (mmol/treatment)	237.3±163.8	511±165.9	<0.001
Diffusive IMB (mmol/treatment)	-84.7±66.7	132.4±98.3	<0.001
Inter-dialytic weight gain (kg)	2.4±1.1	2.7±1.0	NS
Decline in relative blood volume (%)	-8.1±3.5	-7.7±3.6	NS
Pre-dialytic systolic BP (mmHg)	138.6±23.8	147.4±21.2	<0.05
Pre-dialytic diastolic BP (mmHg)	75.2±13.3	81.0±13.6	<0.01

PC=plasma conductivity (mS/cm); IMB=ionic mass balance (mmol/treatment); BP=blood pressure (mmHg)

There were no significant differences in inter-dialytic weight gain (2.6 ± 1.0 versus 2.5 ± 1.0 l), systolic (148.6 ± 25.1 versus 145.5 ± 24.3 mmHg) or diastolic blood pressure (80.5 ± 13.5 versus 79.6 ± 14.4 mmHg) in the period *after* the highest and lowest pre-dialytic PC.

When using univariate analysis with correction for covariates, the difference between the treatments with lowest or highest pre-dialytic PC value and pre-dialytic systolic blood pressure remained significant ($F=5.9$; $P<0.05$) independent of the season ($F=8.38$; $P<0.01$), timing of the dialysis shift [after long or short interval] ($F=0.27$; $P=NS$) and interdialytic weight gain (in the period before the lowest or highest PC) ($F=3.03$; $P=0.08$). The same held true for the difference in pre-dialytic diastolic blood pressure between the treatments with the highest and lowest pre-dialytic PC ($F=6.91$; $P=0.01$) when corrected for inter-dialytic weight gain ($F=4.13$; $P<0.05$), timing of dialysis shift ($F=0.86$; $P=NS$) or season ($F=2.91$; $P=0.09$).

Plasma sodium: variation and relation with PC and IMB

Mean pre-dialytic plasma sodium was 140.0 ± 3.4 mmol/l. Mean intra-individual coefficient of variation was 1.4%. The mean difference between the lowest and highest plasma sodium concentration was 4.6 mmol/l.

In the present study, the relation between pre-dialytic plasma sodium and PC was highly significant ($r=0.77$; $P<0.001$) [Figure 4.4A]. The regression equation between plasma sodium and PC was as follows:

$$\text{plasma sodium} = 26.98 + 7.94 \times \text{PC}$$

(in which a PC of 14.0 mS/cm would correspond to a plasma sodium of 138.1 mmol/l. Using the data of the 332 treatments for which plasma sodium was available, pre-dialytic plasma sodium was significantly related to diffusive IMB ($r=0.57$; $P<0.001$) and total IMB ($r=0.26$; $P<0.001$) (Figure 4.4B).

Validation study: relation between IMB and sodium balance

As displayed in Figure 4.5A a highly significant relation was observed between IMB and sodium balance (using flame photometry) based on direct dialysis quantification ($r^2=0.98$). The disagreement in absolute values appeared to increase at higher levels of IMB, as shown in Figure 4.5B. However, the F-value for the regression equation between sodium balance and IMB was very high ($F=307.6$), with the following equation:

$$\text{Sodium balance (mmol)} = 57 + 1.29 \times \text{IMB}.$$

Using indirect ionometry to determine sodium, the correlation became somewhat less strong ($r=0.91$), but the mean difference between both methods was also somewhat less as compared to the flame photometry measurements (76 ± 202 mmol). Whereas in multiregression analysis, the relation between IMB and sodium balance was highly

significant, the balance of the other ions such as potassium, chloride, bicarbonate and calcium was not significantly related to IMB.

Figure 4.3 A: Relation between pre-dialytic PC and pre-dialytic systolic BP (mean of pooled data)
B: Intra-patient difference in systolic BP between treatments with the lowest and highest PC before dialysis. PC=plasma conductivity (mS/cm); BP=Blood Pressure (mmHg).

Figure 4.4A Relation between pre-dialytic plasma sodium and plasma conductivity
PC=plasma conductivity (mS/cm)

Figure 4.4B Relation between pre-dialytic plasma sodium and diffusive ionic mass balance.
IMB=ionic mass balance (mmol/treatment)

Figure 4.5 A: Relation between IMB by Diascan® and sodium balance by flame photometry in direct dialysis quantification.
B: Agreement between IMB by Diascan® and sodium balance by flame photometry in direct dialysis quantification.
IMB= Ionic mass balance (mmol/treatment); Sodium balance (difference between dialysate inlet sodium and dialysate outlet sodium).

Discussion

This study shows that both intra- and inter-individual variations in PC, which was used as a surrogate for plasma sodium, have a significant effect on IMB (as a surrogate marker for sodium balance) during dialysis. With a dialysate sodium concentration of 140 mmol/l, in a significant percentage of patients diffusive ionic mass transfer from dialysate to patient was observed, whereas PC increased during dialysis in a lesser percentage of patients. Both inter- and intra-individual variations in pre-dialytic PC were related to pre-dialytic blood pressure, independent of interdialytic weight gain and thus appear to be of physiologic relevance.

In agreement with earlier studies in dialysis patients, we observed a significant *inter*-individual variation in pre-dialytic PC, as a surrogate for plasma sodium. Moreover, also significant *intra*-individual variations in PC were observed. In 10 nondiabetic dialysis patients whom were followed for 12 months, Flanigan observed a variation in plasma sodium concentrations of approximately 2%¹¹. This would appear in agreement with the mean coefficient of variation of 1.3% of PC in the present study, which is in agreement with data from the normal population in the literature and likely reflects for the largest part “real” intra-individual and not method variation¹⁵. However, the mean intra-individual difference in PC measurements between the lowest and highest PC measurements during the 6 months follow-up period was 0.9 mS/cm, corresponding to a plasma sodium concentration of ± 9 mmol/l. This observation shows that during a follow-up period of 6 months, relatively large intra-patient variations in PC may occur. Although some of these values may be outliers, they still might have pathophysiologic relevance due to the relation with blood pressure and IMB. We were not able to provide a definite explanation for the variations in PC. He et al. showed an effect of dietary sodium intake on plasma sodium levels¹⁶. We also noted some seasonal variation in PC, although the study was not specifically designed for this purpose. The seasonal variation in PC is in agreement with the data of Chen¹⁷ in peritoneal dialysis patients.

The variation in PC is in agreement with earlier observations on plasma sodium. In the study of Flanigan, the variation in pre-dialytic plasma sodium concentrations was often in the order of 5 mmol/l during the 12 month follow-up period. In the present study, the mean range in plasma sodium levels, which were however only available on a monthly basis, was 4.6 mmol/l.

Various authors suggested the presence of an individual sodium setpoint in dialysis patients, which may be used as a tool for individualized sodium prescription^{6,13,18}. Data on the presence of a fixed sodium setpoint in individual dialysis patients are somewhat conflicting. Whereas some authors did not observe change in pre-dialytic plasma sodium concentration after changing dialysate sodium prescription¹⁸⁻²⁰, we and others observed a change in pre-dialytic PC or plasma sodium after a change in

dialysate sodium prescription^{5,9,21}. The reason for this discrepancy is not clear, but it might also be hypothesized that the patients who experience an increase in plasma sodium level after an increase in dialysate sodium, managed to comply with the habitual fluid restriction, at the cost of increased thirst. The results of the present study suggest that plasma sodium levels, when used as a guide for individualisation of dialysate sodium prescription, should be examined on a regular basis. However, it cannot be excluded that variations in other ions, such as potassium and bicarbonate, also play a role in the observed variations in PC, although e.g. potassium in a concentration of 2 mmol/l contributes only for 0.5% to dialysate conductivity⁸.

Pre dialytic PC was a strong determinant of diffusive IMB, and in a lesser degree to total IMB, during dialysis. Using the mean of 6 months, diffusive IMB was negative in nearly 33% of dialysis patients, suggesting diffusive ionic influx from dialysate to the patient. Due to the strong correlation between IMB and sodium balance⁶ this might suggest net diffusive sodium influx from dialysate to the patient. However, these results should be interpreted with some caution given the fact that sodium removal may be somewhat underestimated by IMB⁶. Surprisingly, we did not observe a mean diffusive ionic influx in the patients treated with Hemocontrol®, which is likely due to the fact that mean PC was higher in these patients. For this observation, we do not have a good explanation. In an earlier randomized crossover study, we observed no difference in IMB of PC when patients were treated with either Hemocontrol® or standard dialysis⁵.

In the present study, we compared IMB measurements to sodium balance using direct dialysis quantification. A highly significant relation was observed between IMB and direct dialysis quantification with sodium measurements assessed by flame photometry.

However, also in our study, some underestimation of sodium removal by IMB was observed. Mass balances of other ions, such as potassium or bicarbonate, were not significantly related to IMB. Access recirculation, which theoretically could also affect IMB measurements was not assessed in the study. However, given the highly significant regression model between IMB and sodium balance, we believe IMB might be used as a indicative marker for sodium balance, taking the caveats into account. In an earlier study, large differences in IMB were observed between treatments which only differed in dialysate sodium prescription⁴.

Averaged over the 6-months period, PC increased during dialysis in 14% of patients, which is an additional argument for diffusive sodium influx in a significant minority of dialysis patients. In general, diffusive ionic influx appeared to occur when pre-dialytic PC was below 14.25 mS/cm (roughly corresponding to a plasma sodium concentration of 140 mmol/l)^{22,23}. However, given the slight underestimation of sodium removal by IMB and the possible effect of other ions on IMB, the extrapolation of these findings

should be interpreted with some caution. Interestingly, the number of patients in which PC increased during dialysis was less compared to the number of patients with diffusive ionic influx. Although the reason for this observation is not entirely clear, this might be due to the fact that to decrease in PC may to some degree, also be due to lowered plasma levels of other ions.

Although far less treatments in which pre-dialytic plasma sodium levels were observed were available for analysis, diffusive ionic influx (negative IMB) from dialysate to patient appeared to occur when plasma sodium concentration was below 140 mmol/l, which would appear in basic agreement with the relation between PC and diffusive IMB discussed above.

Due to the strong influence of ultrafiltration on ionic mass removal, net ionic mass removal was observed in nearly all patients. Admittedly, the clinical importance of the diffusive ionic mass transfer cannot be elucidated from the present study. Lowering of dialysate sodium from 141 to 138 mmol/l at a facility level resulted in a small improvement in BP control without an increase in hypotensive episodes²⁴. Individualisation of dialysate sodium concentration in patients with lower pre-dialytic plasma sodium concentrations was shown to have additive value in terms of blood pressure control¹⁸.

Apart from the effects on diffusive IMB, *intra*-individual differences in PC might be of physiologic relevance, given the significant relation with pre-dialytic systolic BP. This relation was independent from interdialytic weight gain, suggesting an independent pressor effect of plasma sodium, although these observations should be confirmed in future studies as a causal relationship cannot be deduced from the present observational data. Proposed pathophysiological mechanisms for this relation remain hypothetical, and include, among others, an effect of sodium on sympathetic activity, nitric oxide metabolism, or digoxin-like factors^{24,25}. The effect of seasonal variations, which also might influence blood pressure levels, did not explain the relation between PC and blood pressure in our study. As plasma sodium may be decreased in patients with heart failure, one could argue however that also differences in cardiac function, leading to low pre-dialytic systolic BP, could also provide an explanation of these findings. We are not able to provide echocardiographic examinations for all patients during the study period. However, differences in cardiac function are unlikely to explain the effect of *intra*-individual differences in PC on blood pressure: both pre-dialytic systolic BP and diastolic BP were significantly different between treatments with the highest and lowest pre-dialytic PC.

An important advantage of the present study is that it comprises a large group of unselected patients, in which measurements of PC, IMB, and relative blood volume were available for every treatment within a 6 months observation interval. A major limitation is the observational nature of the study. Another drawback of the study is

the fact that PC, and not plasma sodium measurements were used. The use of PC as a surrogate for plasma sodium appears justified in view of the strong relation between PC and plasma sodium⁷, and due to the fact that measurements can be obtained automatically from the software of the dialysis module without the need for blood sampling during every dialysis treatment. From a theoretical point of view, both plasma sodium and PC are surrogate markers of plasma osmolality, which is the driving force for thirst. In the present study, plasma sodium and PC were also highly significantly related. However, in view of the possible (minor) contributions of other ions to PC, our findings should be interpreted with caution.

Another drawback of the study is the absence of detailed information on volume status of the patient, alimentary intake, and the absence of ambulatory blood pressure measurements.

Concluding, diffusive ionic mass transfer is strongly dependent upon pre-dialytic PC. A dialysate sodium concentration of 140 mmol/l was associated with diffusive mass transfer from dialysate to patient, and a rise in PC in a significant percentage of patients. Both intra- and inter-patient variations in PC are significantly related to pre-dialytic systolic blood pressure, independent of interdialytic weight gain, which might suggest a volume-independent effect of sodium. The results of this study may provide additional support for the use of dialysate sodium levels at the lower physiologic range and, where necessary, individualization of dialysate sodium levels..

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Chapter 5

**The effect of sodium profiling and
feedback technologies on plasma conductivity and
ionic mass balance: a study in hypotension-prone
dialysis patients**

Karin Moret, Jeroen Aalten, Warmold van den Wall Bake, Paul Gerlag,
Charles Beerenhout, Frank van der Sande, Karel Leunissen, Jeroen Kooman

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Abstract

Background

Sodium profiling improves hemodynamic tolerance in haemodialysis (HD) patients but may also influence sodium homeostasis. Changes in blood volume and plasma conductivity (PC) during HD can be modelled by feedback technology, but their effects on sodium homeostasis are not widely studied.

Methods

This randomized crossover study compared PC and ionic mass balance (IMB) as surrogate markers of sodium balance between standard HD [dialysate conductivity (DC) 14.0 mS/cm], sodium profiling (DC 15.0 - 14.0 mS/cm), blood volume (BV)-controlled and PC-controlled feedback (target: post-HD PC: 14.0 mS/cm) in 10 HD patients with frequent hypotension.

Results

440 treatments were studied. Pre-dialytic PC was significantly higher during sodium profile (14.4 ± 0.2 mS/cm) compared to standard HD (14.2 ± 0.3 mS/cm), and was not different between the other manoeuvres: PC-controlled (14.1 ± 0.3 mS/cm), and BV-controlled feedback (14.2 ± 0.2 mS/cm). Except for the first treatment, during which IMB was lower during the sodium profile, IMB did not differ significantly between the various manoeuvres and was strongly dependent upon ultrafiltration volume and the difference between pre-dialytic PC and DC.

Symptomatic hypotensive episodes occurred least frequently during BV-controlled feedback (8%) compared to the other manoeuvres (standard HD, 16%; sodium profile, 14%; PC-controlled feedback, 17%), but differences were not significant. Inter-dialytic weight gain and pre-dialytic systolic blood pressure did not differ.

Conclusions

Pre-dialytic PC increased during the sodium profile, and did not differ between BV- or PC-controlled feedback compared to standard HD. Thus, it appears that both BV- and PC-controlled feedback can be safely prescribed without substantial salt- and water-loading, at least in the short term. Analysis of IMB is useful to assess differences in sodium balance between single treatment sessions but appears of less value in a steady-state situation.

Introduction

Sodium profiling with a high dialysate sodium concentration is an effective method for the prevention of intra-dialytic hypotension, but also has possible drawbacks such as increased thirst, inter-dialytic weight gain and hypertension^{1,2}. Recently, it has become possible to model the decline in blood volume and changes in plasma conductivity (PC), as a surrogate of plasma sodium, by means of feedback technologies. With blood volume (BV)-controlled feedback technologies, a target for a maximal decline in BV is set, which is achieved by continuous adjustments of ultrafiltration rate and (when using the Hemocontrol[®] module) continuous adjustments of dialysate conductivity in response to measured changes in BV². In the case of PC-controlled feedback, a target for end-dialytic PC is set, and achieved by frequent adjustments of dialysate conductivity during the dialysis sessions, in response to on-line measured changes in PC³⁻⁵. With both BV- and PC-controlled feedback, it is possible to achieve these targets with a high level of precision. Both modalities are theoretically appealing and were shown to be successful in clinical studies³⁻¹⁰, although clinical experience with conductivity-controlled feedback in particular is still limited^{5,10}. Both modalities, however, also have potential caveats. From a theoretical point of view, the frequent adjustments of dialysate conductivity (DC) during BV-controlled feedback may lead to alterations in sodium removal compared to standard dialysis sessions. PC-controlled feedback treatments with generalized pre-set targets (such as a post-dialytic PC of 14.0 mS/cm) may lead to reduced sodium removal in those patients with low pre-dialytic plasma sodium levels. Little data on sodium balance during these different manoeuvres are available in the literature and are, in most cases, based on a limited number of measurements during the study period⁶⁻⁹. By means of assessment of ionic mass balance (IMB) and changes in pre-dialytic PC, it is possible to assess sodium balance during dialysis therapy in a non-invasive way during every dialysis treatment^{3,4,11}. However, although IMB was able to detect differences in sodium transfer during a single treatment session¹¹, its value in assessing chronic changes in sodium balance is not well established. The aim of the present study was to compare the effects of standard dialysis, a sodium with a mean dialysate sodium concentration, and PC- and BV-controlled feedback treatments on PC and IMB, as surrogate parameters for sodium balance.

Subjects and methods

Twelve patients with frequent symptomatic (see definition below) or asymptomatic hypotensive episodes (decline in systolic blood pressure below 100 mmHg) during dialysis (i.e. >2 during 3 weeks before the start of the study) were included in the study. One patient withdrew from the study because of mitral valve surgery, and one patient died from a cardiac arrest. Data from these patients were excluded from the

analysis. All patients had a residual glomerular filtration rate <2 ml/min. The origin of renal failure in the 10 patients who completed the study was diabetes mellitus ($n=4$), cholesterol emboli ($n=1$), chronic glomerulonephritis ($n=3$), hypertensive nephrosclerosis ($n=1$) and chronic interstitial nephritis ($n=1$). Other characteristics of the patients who completed the study are shown in Table 5.1. The study was approved by the Ethics committee of the Maxima Medical Centre. All patients gave written informed consent.

Table 5.1 Patient characteristics.

Age	71 $\pm$ 11
Sex (M/F)	6 / 4
Time on dialysis (months)	24.1 $\pm$ 17.7
Duration of dialysis (hours)	3.9 $\pm$ 0.5
Diabetes mellitus	6 (60%)
Congestive heart failure (NYHA33)	4 (40%)
Use of ACE inhibitors	4 (40%)
Kt/V (single pool)	1.5 $\pm$ 0.2
Serum albumin (g/l)	38.2 $\pm$ 3.8

Design

All patients were treated with standard HD treatment (DC 14.0 mS/cm), a linear decreasing sodium profile (DC 15.0 - 14.0 mS/cm), BV-controlled feedback (mean DC 14.0 mS/cm) and PC-controlled feedback (target: post-dialytic PC 14.0 mS/cm). The treatment order was prescribed en blocs using a four-treatments, four-period randomized cross-over design. Patients were randomized into one of the following treatment blocks:

- I standard dialysis – sodium profile – BV-controlled feedback – PC-controlled feedback;
- II sodium profile – BV-controlled feedback – PC-controlled feedback – standard dialysis;
- III BV-controlled feedback – PC-controlled feedback – standard dialysis – sodium profile; or
- IV PC-controlled feedback – standard dialysis – sodium profile – BV-controlled feedback.

During each block, patients received 11 consecutive treatments of this modality, followed by 1 week's treatment with standard dialysis in order to prevent possible carry-over effects, after which 11 treatments with the following modality were started, etc. Total duration of the study was 4 months.

Dialysis schedule

The dialysis schedule of the patients was 3 times weekly in all patients. Dialysis time is mentioned in Table 5.1. Polysulfone (F8HPS; Fresenius®) low flux dialysis membranes

were used. Composition of the dialysate was: potassium 2.0 mmol/l, calcium 1.5 mmol/l, magnesium 0.5 mmol/l, bicarbonate 32 mmol/l, acetate 3.0 mmol/l and glucose 1 g/l. Temperature of the dialysate was 36°C. Patients were ultrafiltered until their clinically determined dry weight.

Ionic mass balance

IMB was estimated by Diascan® (Hospal-Gambro®, Lyon, France)^{4,11,12}. In short, Diascan® measures IMB by constant measurement of the conductivity in the dialysis outlet and inlet according to the formula $IMB = [(Qd_{out} \times Cd_{out} - (Qd_{in} \times Cd_{in})) \times 10 \times \text{time (min)}]$. Qd_{out} and Qd_{in} are dialysate flow at, respectively, outlet and inlet; Cd_{out} and Cd_{in} are dialysate conductivity at, respectively, outlet and inlet. A positive IMB reflects net sodium removal from the patient, a negative IMB means net sodium transfer from dialysate to the patient.

Plasma conductivity

PC was measured by Diascan® by measuring dialysance (D) in combination with measurements of Cd_{out} and Cd_{in} according to the formula:

$$PC = [Cd_{out} - (1 - D/Qd_{in}) \times Cd_{in}] / (D/Qd_{in}).$$

D is assessed every 30 min by measuring the increase in Cd_{out} after a temporary increase in Cd_{in} by 1 mS/cm according to the formula:

$$D = (Qd_{in} + Qf) \times [1 - (Cd_{out1} - Cd_{out2}) / (Cd_{in1} - Cd_{in2})].$$

1 and 2 indicate, respectively, the measurements before and after the temporary increase in Cd_{in} ^{4,11,12}.

Relative blood volume

BV was measured continuously by continuous optical assessment of changes in hemoglobin during the dialysis session (Hemoscan®; Hospal-Gambro)¹³.

Description of the feedback modules

BV-controlled feedback (Hemocontrol®; Hospal-Gambro), described in detail elsewhere⁶, is achieved with a closed-loop automatic control system using three controlled variables and two control variables. The three controlled variables are total weight loss (TWL), BV change (determined by hematocrit measurements), and equivalent conductivity, a value derived from the DC which is defined as the conductivity value required to achieve the same sodium mass balance compared to standard HD⁶. The control variables consist of the set ultrafiltration rate (UFR) and the delivered DC. Discrepancies between ideal and achieved controlled variable values are processed by a multi-input/multi-output controller that in turn effectuates a response through the two actuators, the control variables UFR and DC. Changes in BV are

determined by Hemoscan® (see above). TWL is measured volumetrically. Before the start of the study, the patient underwent 10 regular treatments. During this period, the mean BV change at which hypotension occurred was recorded. The target BV:TWL ratio during BV-controlled feedback was 20% higher than this value.

With PC-controlled feedback (Diacontrol®; Hospal-Gambro), PC is modelled automatically during dialysis by adjustment of DC using single-pool kinetic modelling^{4,5}. PC is measured throughout the HD session by Diascan® as described above. The target post-dialytic PC was 14.0 mS/cm during all treatment sessions.

Plasma sodium

Plasma sodium was assessed by indirect ionometry (Vitros 950®), which assesses sodium activity in the plasma. Sodium activity is automatically converted to the molar ionized sodium concentration. Obtained values were corrected by converting the molar concentration to flame photometer values by a standard correction factor (0.93)¹⁰. The coefficient of variation for this method, as given by the manufacturer, is 0.4%.

Blood pressure measurements

Blood pressure was assessed every 30 min with an oscillometric device (HDBPM 4; Hospal-Gambro). Also during each symptomatic event, blood pressure was measured.

Definition of intra-dialytic hypotension

Symptomatic hypotension was defined as a decline in systolic blood pressure to <100 mmHg (in patients with pre-dialytic systolic blood pressure <110 mmHg), or a decline in systolic blood pressure larger than 30 mmHg together with typical symptoms, necessitating nursing interventions. Also all intra-dialytic morbid events (cramps, nausea, headache, abdominal pain, with or without hypotension) were recorded. Also all episodes with a decline in systolic pressure below 100 mmHg were recorded.

Power analysis

Primary outcome parameter was the difference in pre-dialytic PC between the various modalities. Assuming an SD of 0.2 mS/cm¹¹, eight patients would be needed to show a mean difference of 0.2 mS/cm between two different treatment modalities with a level below 0.05 and a power of 0.80. Assuming an SD of 110 mmol for IMB¹¹, nine patients had to be included in order to show a difference of 100 mmol with the same significance levels. In order to correct for multiple comparisons and drop-outs, 12 patients were included.

Statistics

Repeated measurements ANOVA was used to compare the different parameters between the various modalities. The mean value of the 11 treatments for each modality was entered into the analysis. To assess the determinants of IMB, multiregression analysis was used. Fisher's exact-test was used to assess differences in frequency of hypotension between the different modalities. *P*-values <0.05 were considered significant. The SPSS 12.0 package was used for statistical analysis.

Results

Data for IMB and PC were available for all sessions. In total, data of 440 sessions were analyzed.

Plasma conductivity

Mean pre- and post-dialytic PC were increased during the sodium profile compared to standard HD. Pre-dialytic PC did not differ between BV- and PC-controlled feedback compared to standard HD (Figure 5.1 and Table 5.2). Post-dialytic PC was significantly lower during PC-controlled feedback compared to the other manoeuvres.

Figure 5.1 Pre- and post-dialytic PC levels during the different modalities. Covered boxes indicate 25–75% with median value; capped bars indicate the range of data. Dots indicate outliers. Both pre- and post-dialytic PC were significantly higher during the sodium profile compared to all other treatments ($P<0.05$). Post-dialytic PC was significantly lower during PC-controlled feedback compared to the other manoeuvres.

Table 5.2

	Standard	BV-feedback	PC-feedback	Sodium profile
Pre-dialytic PC (mS/cm) ^a	14.22 ± 0.20	14.22 ± 0.17	14.14 ± 0.22	14.37 ± 0.14b
Post-dialytic PC (mS/cm) ^a	14.11 ± 0.20c	14.11 ± 0.10c	14.03 ± 0.04b,c	14.42 ± 0.05b
DC (mS/cm) ^a	14.06 ± 0.06	14.23 ± 0.04b	14.03 ± 0.12	14.42 ± 0.05b
Ionic mass removal (mmol)	383 ± 112	432 ± 80	370 ± 140	414 ± 106
IDWG	2.0 ± 1.0	2.2 ± 0.7	2.0 ± 0.9	2.1 ± 1.0
Decline in relative BV (%)	-6.1 ± 2.4	-6.6 ± 2.3	-6.4 ± 3.1	-7.4 ± 2.1
Pre-dialytic SBP (mmHg)	146 ± 26	140 ± 23	145 ± 19	144 ± 22
Nadir dialytic SBP (mmHg)	111 ± 22	108 ± 19	111 ± 17	112 ± 18
Post-dialytic weight (kg)	76.8 ± 14.2	76.1 ± 16.0	76.1 ± 14.8	76.5 ± 14.6

PC, plasma conductivity; DC, dialysate conductivity; IDWG, inter-dialytic weight gain; SBP, systolic blood pressure; BV, blood volume. ^a $P < 0.05$ (ANOVA); ^b $P < 0.001$ compared to all other treatments; ^c $P < 0.001$ compared to pre-dialytic values.

PC-controlled feedback was able to reach target post-dialytic PC levels within narrow limits (14.03±0.03 mS/cm). In those sessions in which pre-dialytic plasma conductivity levels were <14.0 mS/cm, as expected, PC increased significantly (+0.21±0.17; $P < 0.001$) and declined during sessions when pre-dialytic PC was >14.0 mS/cm (-0.18±0.14; $P < 0.001$). During PC-controlled feedback, the intra-individual coefficient of variation of pre-dialytic PC levels was 1.3%. Pre-dialytic PC varied between values above and below 14.0 mS/cm in six of the patients during the period with PC-controlled feedback.

Single measurements of pre-dialytic plasma sodium did not differ between the different modalities: 138±2 mmol/l during standard dialysis, 137±2 mmol/l during BV-controlled feedback, 139±3 mmol/l during the sodium profile and 138±3 mmol/l during PC conductivity-controlled feedback.

Ionic mass balance

IMB during the first session was lowest during the sodium profile (315±157 mmol; $P < 0.05$). Between the other manoeuvres, IMB during the first sessions did not differ: 423±166 mmol during standard dialysis, 488±179 mmol during BV-controlled feedback and 409±109 mmol during PC-controlled feedback.

During the remainder of the sessions, IMB did not differ significantly between the different treatment modalities (Table 5.2).

However, during PC-controlled feedback, IMB was lower during the sessions when pre-dialytic PC was lower than 14.0 mS/cm ($n=30$) compared to sessions before which pre-dialytic PC was higher than 14.0 mS/cm ($n=80$). (248±98 vs 416±174 mmol/l; $P < 0.001$) despite comparable ultrafiltration volume (2.0±0.7 vs 2.0±1.1 kg).

Pooling all treatments, ionic mass removal was highly dependent upon both ultrafiltration volume ($\beta=0.72$; $P < 0.001$) and the difference between pre-dialytic

plasma conductivity and dialysate conductivity ($\beta=0.72$; $P<0.001$) (Figure 5.2), but not on the treatment modality.

Figure 5.2 Relation between ionic mass balance and pre-dialytic and dialysate conductivity. ($r^2=-0.46$; $P<0.001$).

Inter-dialytic weight gain and blood pressure and blood volume

Neither inter-dialytic weight gain nor pre-dialytic blood pressure differed significantly between the various treatment modalities (Table 5.2). Also post-dialytic blood pressure and the maximal decline in blood pressure were not significantly different between the various treatment modalities. The decline in BV was comparable between the various treatment modalities (Table 5.2).

Intra-dialytic hypotension

Symptomatic hypotensive episodes occurred least frequently during BV-controlled feedback (8%) compared to the other manoeuvres (standard HD, 16%; sodium profile, 14%; PC-controlled feedback, 17%), but differences were not significant. The same held true for the total number of symptoms during dialysis (with or without hypotension): BV-controlled feedback, $n=22$; standard HD, $n=31$; sodium profile, $n=29$; PC-controlled feedback, $n=32$ ($P=NS$). The total number of sessions during which systolic BP declined to <100 mmHg did not differ significantly between the different manoeuvres: BV-controlled feedback, 26%; standard HD, 35%; sodium profile, 28%; PC-controlled feedback, 26% ($P=NS$).

The peak systolic blood pressure did not differ between the various sessions (Table 5.2).

Discussion

In this randomized crossover study, we assessed the effect of a sodium profile and different feedback technologies on PC, IMB and haemodynamic tolerance. A significant increase in pre-dialytic PC was observed during the sodium profile, but not during BV-controlled feedback, whereas pre-dialytic PC was not different during PC-controlled feedback compared to standard HD.

IMB was lowest during the sodium profile, but only during the first session, and not during the remainder of the dialysis sessions with the sodium profile. IMB during the other modalities was comparable. The increase in pre- and post-dialytic PC, as surrogate markers of plasma sodium, is in agreement with various, but not all, earlier studies towards the effect of profiles with high mean sodium concentrations^{1,2}.

The effects of BV-controlled feedback on PC and IMB did not differ from standard dialysis. Data on the effects of BV-controlled feedback on sodium homeostasis are scarce, although earlier studies did not show a difference in plasma sodium levels compared to standard HD sessions. However, in these studies, serum sodium was only measured a few times during the study period, whereas in the present study, PC was assessed during all treatment sessions.

With PC-controlled feedback, mean pre-dialytic PC was not different compared to standard dialysis. However, mean post-dialytic PC was significantly lower compared to standard HD. The target post-dialytic PC was 14.0 mS/cm in the present study. In agreement with earlier data from Locatelli *et al.*¹⁰, PC-controlled feedback was able to achieve this target within very narrow limits. However, caution should be applied with the use of PC-controlled feedback with generalized preset targets in patients with low pre-dialytic PC levels. An alternative approach given the intra-individual variation of predialytic PC or sodium levels may be the use of individualized targets for dialysate sodium or post-dialytic PC^{10,11,14}.

IMB was only significantly different between the first sessions of the different modalities, and not during the remaining sessions. This can be explained by the fact that, next to ultrafiltration volume, IMB is determined by the ratio between predialytic PC and dialysate conductivity¹¹. Thus, as pre-dialytic PC increased during the sodium profile, the difference between PC and DC remained comparable to the other modalities, resulting in equal IMB. Therefore, the absence of differences in IMB between different dialysis modalities in a steady state does not imply that these do not differ in their effect on sodium balance. To estimate such an effect, measurement of plasma sodium or PC levels remains necessary.

However, during PC conductivity-controlled feedback, IMB was lower when pre-dialytic PC was <14.0 mS/cm compared with pre-dialytic PC levels >14.0 mS/cm. This is

due to the strong relation between pre-dialytic PC and dialysate conductivity. As in the majority of patients, pre-dialytic PC levels varied between values above and below 14.0 mS/cm, IMB may be unpredictable when using generalized pre-set targets, as discussed previously.

Despite differences in pre-dialytic PC, pre-dialytic blood pressure and inter-dialytic weight gain did not differ between the different treatment modalities. However, small effects on inter-dialytic blood pressure may have been missed in the present study, due to the absence of ambulatory blood pressure measurements.

The effect of sodium profiling on inter-dialytic weight gain and inter-dialytic blood pressure control is not consistent between different studies. Whereas some studies found an increase in inter-dialytic weight gain and/or an increase in pre-dialytic systolic or inter-dialytic blood pressure, other studies did not^{1,2}.

A potential explanation for the absence of a difference in weight gain or blood pressure control between the various modalities may be strict adherence to fluid restriction by our patients. Regrettably, thirst sensation was not quantified in a structured way in the present study.

The incidence of symptomatic intra-dialytic hypotension was lowest during BV-controlled feedback, but differences between the various manoeuvres did not reach significance, due to underpowering of the study for this parameter. Earlier studies with larger number of patients have demonstrated the effect of BV-controlled feedback on intra-dialytic complications^{6,7,15–17}.

Except for the possible underpowering with respect to the secondary outcome parameter of intra-dialytic hypotension, some other drawbacks should also be mentioned. Firstly, PC and not plasma sodium was assessed in the present study, due to the fact that this parameter can be assessed on-line without need for blood sampling. Previous studies have shown a very close correlation between PC and plasma sodium levels^{11,18,19}. However, PC is not equal to plasma sodium and, albeit to a much smaller degree, is also influenced by other electrolytes such as potassium. This might be reflected in the fact that post-dialytic PC was lower than pre-dialytic PC during all different modalities. From a theoretical point of view, differences in potassium and acid base balance are not to be expected between the different dialysis strategies studied in this paper. Indeed, frequent measurements of PC may be more sensitive in observing differences in sodium balance than single measurements of plasma sodium. In the present study, single measurements of plasma sodium did not differ between the various modalities.

Lastly, the sodium profile used in the present study is only an example of many different sodium profiles described in the literature². However, in the majority of effective sodium profiles high dialysate sodium concentrations are used.

Summarizing, pre- and post-dialytic PC, as a surrogate marker of plasma sodium, increased during high-sodium profiling, but not during BV- or PC-controlled feedback treatments. Thus, it appears that both BV- and PC-controlled feedback can be safely prescribed without substantial salt- and water-loading, at least in the short term.

Except for the first treatment, IMB did not differ between the various manoeuvres, due to the equilibration between pre-dialytic PC and DC. Therefore, IMB appears of limited value to assess differences in sodium balance between different manoeuvres in steady state.

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Chapter 6

**Conductivitypulses needed for Diascan[®]
measurements: Does it cause sodium burden?**

Karin Moret, Diana C Grootendorst, Charles Beerenhout, Jeroen P Kooman

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Recently, new techniques based on conductivity measurement enable the physician to evaluate the adequacy of hemodialysis dose (HDD) on all haemodialysis treatments by on-line monitoring of KT/V. Ionic dialysance (Diascan® Hospal®) is a parameter calculated from the dialysate conductivity at the dialyser inlet and outlet. Every half hour the inlet dialysate conductivity increases by 1 ms/cm during 5 minutes while the outlet dialysate conductivity-cell measures the effect of this increase. The calculated ion transfer across the membrane (largely sodium) is almost equivalent to urea transfer and therefore ionic dialysance reflects the urea clearance. This method has a good correlation with Kt/V measured by the mathematical urea equations in several studies^{1,2,3,4}.

However, some investigators suggest, that during the conductivity pulse of 5 minutes, significant amounts of sodium may be transferred into the patient⁵. In our centre we studied that effect. Diascan® also measures Ionic Mass Balance (IMB) and plasma conductivity (PC) which are likely to represent sodium balance and plasma sodium respectively (Plasma sodium in mmol/l $\approx$ plasma conductivity in ms/cm * 10). This is performed by constant measurements of the conductivity in the dialysate inlet and outlet, according to the formulas:

$$PC = [Cd_{out} - (1 - D/Qd_{in}) \times Cd_{in}] / (D / Qd_{in})$$

Qd_{in} and Qd_{out} are dialysate flow at, respectively, inlet and outlet. Cd_{in} and Cd_{out} are dialysate conductivity at, respectively, inlet and outlet. D is Ionic Dialysance.

$$IMB = [(Qd_{out} \times Cd_{out}) - (Qd_{in} \times Cd_{in})] \times 10 \times \text{time (min)}.$$

A positive IMB means sodium removal from the patient. A negative IMB means sodium transport to the patient.

In patients with zero inter-dialytic weight gain, IMB was measured in 200 isovolemic hemodialysis sessions by Diascan®, 137 sessions were performed with 4-8 conductivity pulses. 63 sessions were performed with only 1 conductivity pulse.

The results were that there was a highly significant correlation between pre-dialytic plasma conductivity and IMB (Spearman rank $r_s = 0.902$, $P < 0.005$), in agreement with previous studies⁶. There was no correlation between IMB and the number of conductivity pulses (Spearman rank $r_s = 0.02$, $P = 0.328$) (Figure 6.1).

Figure 6.1 Correlation between IMB during isovolaemic haemodialysis and number of conductivity pulses.

In conclusion, Diascan® is a useful tool to assess dialysis dose without evidence of an increased sodium load related to the conductivity pulses during hemodialysis treatment.

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Chapter 7

Agreement between different parameters of dialysis dose in achieving treatment targets: results from the NECOSAD study

Karin E Moret, Diana C Grootendorst, Friedo W Dekker, Elizabeth W Boeschoten, Raymond T Krediet, Saskia Houterman, Charles H Beerenhout, Jeroen P Kooman, the NECOSAD Study Group

Submitted

Abstract

Background

The recommended parameter of dialysis dose differs between K-DOQI and EBPG guidelines. It is not well known to which extent agreement between the different parameters exists if target and delivered dialysis dose are prescribed according to urea reduction rate (URR), single pool Kt/V (spKt/V) or equilibrated double pool Kt/V (eKt/V), and which parameter is most strongly related to mortality.

Methods

In 830 hemodialysis patients from the NECOSAD cohort URR, spKt/V and eKt/V were calculated and compared according to classification regarding the recommended treatment targets (70%, 1.4 and 1.2, respectively), as well as minimum delivered dialysis dose (65%, 1.2 and 1.05, respectively). Moreover, the relation between treatment dose and survival was assessed using Cox regression analysis.

Results

A spKt/V of ≥ 1.4 and $URR \geq 70\%$ corresponded with $eKt/V \geq 1.20$ (as reference method) in respectively 98.0% and 90.6% of patients. spKt/V of ≥ 1.2 and $URR \geq 65\%$ corresponded with $eKt/V \geq 1.05$ in respectively 95.5% and 91.2% of patients. Deviations from the reference method were significantly related to differences in urea distribution volume (spKt/V), treatment time (URR) and ultrafiltration volume (URR). Adjusted HR (95%CI) was 0.98 (0.96, 0.99) for URR, 0.51 (0.31, 0.84) for spKt/V and 0.46 (0.30, 0.80) for eKt/V.

Conclusion

Use of URR leads to larger disagreement with the reference method (eKt/V) treatment target as compared to spKt/V. Low urea distribution volume, short treatment time, and low ultrafiltration volumes are predictive parameters for overestimation of dialysis dose when utilizing the alternative methods spKt/V and URR instead of eKt/V. Delivered eKt/V, spKt/V, and URR were all positively related to survival. However, only in case of eKt/V, the minimum cut-off level was predictive of survival.

Introduction

The delivered haemodialysis treatment dose is an important prognostic factor in patients treated with haemodialysis¹. In addition, a survey of the medical literature reported an increase in the quality-adjusted life expectancy of haemodialysis patients with increasing dialysis adequacy².

To determine dialysis adequacy, various methods are currently used. The most simple marker is the urea reduction rate (URR) for which only the pre- and post-dialytic blood urea concentrations are needed. However, the use of URR does not take the effects of ultrafiltration on urea removal into account, nor the effect of urea generation during dialysis. These factors are integrated when the formula of single pool Kt/V_{urea} (spKt/V) is used to assess dialysis adequacy. The calculation of spKt/V is somewhat more elaborate, as data of body weight, type of vascular access, treatment time and ultrafiltration volume are needed. However, with spKt/V, the effect of urea rebound from the peripheral tissues to the blood is neglected. For this purpose, the formula of equilibrated double pool Kt/V (eKt/V) was developed, which corresponds to spKt/V with 30 minutes urea rebound. For computation of eKt/V, no additional parameters in addition to those needed for calculation of spKt/V are required, although the formula is slightly more complicated compared to spKt/V.

Various guidelines groups have defined targets for dialysis dose prescription^{3,4}. K/DOQI guidelines recommend measurement of haemodialysis dose using spKt/V, whereas EBPG guidelines prefer using eKt/V^{3,4}. In addition, some national registries, such as the UK Renal Registry [6], advocate the use of URR to assess dialysis adequacy. However, despite the fact that the EBPG on dialysis adequacy have been published various years ago, a recent survey by the EDTA-QUEST [5] initiative showed that URR (46%), followed by spKt/V (35%), was used in a great majority of dialysis centers in daily practice. eKt/V was used by only 13% of respondents.

The primary aim of our study was to determine the agreement between URR, spKt/V and eKt/V in the assessment of dialysis adequacy, taking the different cut-off values for these parameters into account. Second, to determine factors for disagreement, considering eKt/V as gold standard. Third, the relation to survival in URR, spKt/V and eKt/V was assessed.

Subjects and Methods

Patients

Patients with end stage renal disease starting dialysis treatment in 38 dialysis centres in The Netherlands were invited to participate in the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) study. Recruitment of patients was between August 1996 and March 2007. Inclusion criteria were age ≥ 18 years and starting renal

replacement therapy for the first time. Additional criteria for the present analysis were treatment with haemodialysis at twelve months after the start of dialysis (n=1122) and complete data for the measurement of dialysis adequacy (n=830). The study was approved by the Medical Ethics Committees of all participating hospitals. All patients gave written informed consent.

Design

At start of dialysis, data regarding clinical and demographic characteristics, including gender, age, smoking status, primary kidney disease and co-morbidity, were collected. Patients were followed at three and six months after start of dialysis treatment, thereafter at 6-monthly intervals. Data for dialysis adequacy were collected at 12 months after the start of dialysis, because stability in haemodialysis treatment may be assumed (and the contribution of residual renal function may be less prominent as compared to the 3 and 6 months data). Body weight was measured before and after each haemodialysis session. Treatment characteristics collected were dialysis frequency, ultrafiltration volume and treatment time. Blood samples were drawn before and after a monitoring dialysis session and again before the following dialysis session. Urine was collected during the entire interdialytic interval. Follow-up was until time of death, transplantation, transfer to a non-participating hospital, recovery of renal function or end of study (20 August 2007). Follow-up was censored to a maximum of 5 years.

Data collection

Demographic and baseline data were obtained 0 to 4 weeks before the start of chronic dialysis treatment. Comorbidities were scored in case of presence of a doctors diagnosis. Co-morbidity risk score was assessed as recommended by Khan et al.⁷ Primary kidney disease and cause of death were classified according to the codes of the European Renal Association-Dialysis and Transplantation Association⁸.

Dialysis dose/adequacy

eKt/V was computed using the Daugirdas-Schneditz rate equation (Appendix 1) and considered as golden standard, while spKtV and URR were determined from the pre-n postdialysis blood urea nitrogen (BUN) using the two-BUN method (Appendix 2+3). Urea distribution volume (V) was calculated using Watson's formula (Appendix 4). rGFR was estimated according to the formula in Appendix 5. Since residual renal function may contribute significantly to final weekly Kt/V, the estimation of renal plus dialytic Kt/V allows better judgment of total adequacy. Therefore rKt/V+eKt/V(wk) and rKt/V+spKt/V(wk) were also assessed. eKtV and spKt/V including rGFR were expressed in weekly rKt/V+eKt/V(wk) and subsequently rKt/V+spKt/V(wk) (Appendix 6) to value total treatment dose.

Minimal dialysis adequacy was compared between the minimum aims: $\text{eKt/V} > 1.05$, which is the minimum according to the HEMO study^{9,10}, and to $\text{spKt/V} > 1.2$ and $\text{URR} > 65\%$ (minimum according to K-DOQI)³.

Target dialysis adequacy was compared between the target levels of the different methods: $\text{eKt/V} > 1.20$ (target EBPg 2001), $\text{spKt/V} > 1.40$ and $\text{URR} > 70\%$ (target K-DOQI).

Dialysis adequacy was also categorized in order to enable comparison between the different adequacy formulas with different units. This was achieved by classifying into three categories. The middle category of each of the dialysis adequacy formulas, considered as sufficient dialysis dose and defined as the reference group, was compared to the lowest category (inadequate dialysis) and the highest category (above target dose).

Statistical analysis

Results are expressed as mean $\pm$ SD. Differences in continuous variables were tested using the Students *t* test if normally distributed or Wilcoxon rank-sum test if skewed. The agreement between the different methods was analyzed using linear regression models and descriptive statistics. Crude and adjusted hazard ratios for the different parameters were calculated using Cox proportional-hazards regression modeling. In analogy to the study of Termorshuizen et al.¹¹ age, Khan comorbidity score, primary kidney disease and body mass index were used as covariates. The SPSS-13.0 package was used for statistical analysis. $P \leq 0.05$ was regarded as statistically significant.

Results

A total of 2062 patients were included in the NECOSAD study. 1217 patients started with haemodialysis. In 830 of those, data for dialysis adequacy assessment at 12 months after the start of dialysis were available, and were included in the present analysis.

Baseline characteristics of these patients are listed in Table 7.1. At twelve months after start of dialysis mean age was 64, 41% was female, 21% had diabetes and 74% of the haemodialysis patients were treated three times per week or more. Mean haemodialysis treatment time was 10.29 ± 1.97 hours/week. In Table 7.2 the characteristics of haemodialysis treatment, haemodialysis adequacy, and residual renal function (rGFR) are shown. Residual renal function was present in 522 patients.

Table 7.1 Patient demographics at baseline.

Number of patients, n	830
Age, years	64 (13)
Gender, % male	60
Ethnicity, % Caucasian	92
Weight, kg	73.2 (14.4)
Height, cm	170.5 (9.6)
BMI, kg/m ²	25.2 (4.5)
Primary kidney disease, %	
Diabetes	15
Glomerulonephritis	10
Renal vascular disease	21
Other	54
Diabetes, %*	21
Khan co-morbidity score, %	
Low	32
Medium	38
High	30

Mean values (SD) are presented for continuous variables. * Patients with diabetes either as comorbid condition or primary kidney disease.

Table 7.2 Characteristics of haemodialysis treatment, adequacy and residual renal function.

Treatment time per week, hours	10.29 (1.97)
Dialysis frequency, per week	2.76 (0.48)
UF volume, millilitres	1970 (1184)
eKt/V	1.02 (0.23)
spKt/V	1.18 (0.26)
%URR	63 (8)
rGFR, ml/min	3.69 (1.9)
rKt/V+eKt/V, per week	3.56 (0.86)
rKt/V+spKt/V, per week	3.99 (0.96)
V, litres	37.2 (6.29)

* n=522. Mean values (SD) are presented for continuous variables.

Adequacy of haemodialysis dose

12 months after start of dialysis, mean delivered eKt/V was 1.02 ± 0.23 , spKtV 1.18 ± 0.26 , and URR $63\% \pm 8\%$. Mean rGFR was 3.69 ± 1.9 ml/min/1.73 m² and mean V was 37.2 ± 6.3 liters. Taking rGFR into account, total mean rKt/V+ eKt/V(wk) was 3.56 ± 0.86 and mean rKt/V+spKt/V(wk) 3.99 ± 0.96 (Table 7.2).

Comparison of dialysis adequacy measures

Correlation between spKt/V and eKt/V (Pearson correlation $r=0.99$, $P<0.001$) and URR and eKt/V (Pearson correlation $r=0.95$, $P<0.001$) was highly significant (Figure 7.1). When spKt/V was used, 374 patients reached the **minimal** dose, whereas in 17 (4%) of those minimal eKt/V was not attained (Figure 7.1A). When using the URR equation, in

352 patients dialysis dose attained the minimal criteria, whereas eKt/V showed in 31 (9%) of these patients an inadequate dialysis dose (Figure 7.1B).

Using $eKt/V \geq 1.2$, $spKt/V \geq 1.4$ and $URR \geq 70\%$ as **target** aims for adequate haemodialysis dose, the three different parameters were analyzed. In 161 (19%) of the patients $spKt/V$ dialysis dose was at or above the target range, without residual renal function taking into account. However, three of these patients (2%) did not reach the target level according to eKt/V (<1.2 but >1.19) (Figure 7.1C). When URR was used in the cohort of 830 patients, 160 (19%) patients had a dialysis dose at or above the target range. In fifteen of those (9%), eKt/V was below the target (<1.2 but ≥ 1.08) (Figure 7.1D).

Figure 7.1 Correlation between single pool Kt/V and equilibrated double pool Kt/V ($r=0.994$) and urea reduction rate and equilibrated double pool Kt/V ($r=0.953$). Panel A shows classified and misclassified cases between minimal dose of single pool Kt/V and equilibrated double pool Kt/V, panel B shows classified and misclassified cases between minimal dose of urea reduction rate and equilibrated double pool Kt/V. Panel C shows classified and misclassified cases between target dose of single pool Kt/V and equilibrated double pool Kt/V, panel D shows classified and misclassified cases between target dose of urea reduction rate and equilibrated double pool Kt/V. *The lower right quadrant are the misclassified patients in whom minimal dialysis adequacy is overestimated when making use of the alternative methods

Table 7.3 summarizes differences in characteristics of patients in which dialysis adequacy would be overestimated when alternative methods for estimating dialysis adequacy were used instead of the gold standard. Treatment time and ultrafiltration volume were significantly different at the misclassification when **minimum** dose of URR was reached instead of eKt/V (8.8 vs 10.2 hrs/wk respectively 571 vs 1993 ml/treatment; $P<0.001$). The misclassification using spKt/V instead of eKt/V as minimal cut-off point showed significant differences in treatment time (9.3 vs 10.4 hrs/wk) and urea distribution volume (31.1 vs 34.8 l; $P=0.003$). The disagreement of reaching target dose by the alternative parameters compared to the golden standard showed the same significant characteristics. Treatment time and ultrafiltration volume were significantly different between the classified and misclassified patients when URR was used to judge sufficient dialysis dose instead of eKt/V (8.2 vs 10.2 hrs/wk for treatment time and 330 vs 1916 ml/treatment for ultrafiltration; $P<0.001$). When using spKt/V instead of eKt/V only urea distribution volume obtained statistical significance while defining characteristics of misclassified patients (28.8 vs 33.3 l; $P<0.001$).

Relation of the different treatment indices with mortality

URR, spKt/V and eKt/V were each significantly related to survival, after correction for confounding factors. For each unit increase in dialysis adequacy, the adjusted HR (95%CI) was 0.98 (0.96, 0.99) for URR, 0.51 (0.31, 0.84) for spKt/V and 0.46 (0.30, 0.80) for eKt/V . When dividing the groups into three categories (below minimum, above target, and levels between minimum and target), with the latter as reference, the trends in survival between the different parameters remained, but only reached significance for eKt/V . Patients with eKt/V levels in the lowest category (below minimum) had the highest risk of mortality independent of other factors (Table 7.4).

Table 7.3 Differences in characteristics of patients, classified according to the alternative methods, while misclassified according to ekt/V (considered as gold standard).

	Minimum dose			Minimum dose		
	URR≥65 ektV<1.05 n=31 misclassified	URR≥65 ektV≥1.05 n=321 classified	P-value	spKtV≥1.2 ektV<1.05 n=17 misclassified	spKtV≥1.2 ektV≥1.05 n=357 classified	P-value
Sex (% female)	74	58	0.013*	70.6	54.5	0.076
Dry weight (kg)	66.8	68.3	0.688	65.4	69.2	0.097
Treatment time (hrs/wk)	8.8	10.2	<0.001*	9.3	10.4	0.003*
HD frequency (% 2 x wk)	35	37.8	0.916	11.8	34.8	0.265
UF volume (ml/treatment)	571	1993	<0.001*	1994	2131	0.574
Urea distribution volume (l)	33.3	34.5	0.255	31.1	34.8	<0.001*
Range	ekt/V: 0.93-1.05	ekt/V: 1.05-2.12		ekt/V: 1.01-1.05	ekt/V: 0.93-1.05	
	Target dose			Target dose		
	URR≥70 ektV<1.2 n=14 misclassified	URR≥70 ektV≥1.2 n=145 classified	P-value	URR≥1.4 ektV<1.2 n=3 classified	spKtV≥1.4 ektV≥1.2 n=158 classified	P-value
Sex (% female)	73.3	63.4	0.447	100	63.1	0.187
Dry weight (kg)	63.8	65.3	0.677	58.2	66.1	0.228
Treatment time (hrs/wk)	8.2	10.2	<0.001*	9.5	10.4	0.212
HD frequency (% 2 x wk)	60	42.1	0.379	0	39.2	0.365
UF volume (ml/treatment)	330	1916	<0.001*	1860	2044	0.684
Urea distribution volume (l)	32.0	33.0	0.481	28.8	33.3	0.028*
Range	ekt/V: 1.08-1.19	ekt/V: 1.2-2.12		33.3 ekt/V: 1.17-1.19	ekt/V: 1.2-2.12	

URR=Urea reduction rate in %, ekt/V=equilibrated double pool Kt/V, spKt/V=single pool, kg=kilograms, hrs/wk=hours per week, ml=millilitres, l=litres.

Table 7.4 Crude and adjusted mortality risk (hazard ratio [HR] with 95%CI) for each of the formulas of dialysis adequacy / dose, n=830

	Crude HR (95% CI)	Adjusted HR (95% CI)*
URR	0.99 (0.97, 1.0)	0.98 (0.96, 0.99) [#]
spKt/V	0.72 (0.49, 1.07)	0.51 (0.31, 0.84) [#]
eKt/V	0.67 (0.43, 1.05)	0.46 (0.3, 0.80) [#]

Adequacy formulas divided in categories, according to minimum and target value, with the recommended value as reference category

Adjusted HR (95% CI)*	Category 1 (below minimum)	Category 2 (recommended)	Category 3 (above target)
URR ^a	1.08 (0.82, 1.43)	1.00	0.73 (0.51, 1.04)
spKt/V ^b	1.29 (0.98, 1.69)	1.00	0.86 (0.61, 1.20)
eKt/V ^c	1.46 (1.09, 1.95) [#]	1.00	1.07 (0.75, 1.52)
rKt/V+spKt/V, wk ^b	1.23 (0.92, 1.65)	1.00	0.84 (0.63, 1.12)
rKt/V+eKt/V, wk ^c	1.12 (0.83, 1.51)	1.00	0.77 (0.58, 1.02)

^a1: URR<65 (n=478) 2(reference): 65<URR<70 (n=194) 3: URR>70 (n=158)

^b1: spKt/V<1.2 (n=456) 2(reference): 1.2<spKt/V<1.4 (n=213) 3: spKt/V>1.4 (n=161)

^c1: eKt/V<1.05 (n=472) 2(reference): 1.05<eKt/V<1.2 (n=172) 3: eKt/V>1.2 (n=186)

*HR adjusted for age, Khan co-morbidity score, BMI, primary kidney disease, nutritional status, duration of the dialysis session, and GFR (GFR not for spKt/V(wk) and eKt/V(wk). [#]significant, P<0.05

Discussion

The results of the present study show that minimum dialysis dose will be satisfactory predicted by spKt/V and URR in a majority of patients (96% and 91% respectively), considering eKt/V as gold standard. In a minority of patients, the adequacy minimum for eKt/V was not met, despite the fact that URR and/or spKt/V appeared to be in an acceptable range. The risk of misclassification was higher for URR (9%) compared to spKt/V (4%). All adequacy parameters were significantly related to mortality. However, after categorizing patients according to minimum and target values of the different adequacy parameters, only for eKt/V mortality rates were higher when minimum levels were not met.

There has been ample discussion about the recommended parameter for dialysis dose in various guidelines^{3,4}. Whereas the EBPG recommends the use of eKt/V as the parameter of dialysis dose, spKt/V is advocated by K-DOQI. The rationale for the use of eKt/V by EBPG is based on the fact that urea rebound after dialysis is taken into account by adding a time-dependent factor to the equation¹². Especially in patients treated with very short dialysis sessions, the difference between spKt/V and eKt/V increases, which might result in overestimating dialysis adequacy when dialysis dose is valued by spKt/V². In contrast, the K-DOQI group decided to maintain spKt/V as the recommended parameter of dialysis dose, as shortened dialysis treatment times are not allowed by both K-DOQI and EBPG guidelines, and because eKt/V is a

mathematical derivative of spKt/V , which cannot be adjusted directly by changing treatment parameters³.

In our study, in only 4% of patients with a $\text{spKt/V} \geq 1.2$, eKt/V was lower than 1.05. Moreover, we see in this “misclassified” subgroup a mean eKt/V of 1.03 (<1.05 but >1.01), which is very close to minimum level. The notion that ultrashort dialysis neither was nor is current practice in the Netherlands¹³, explains our observation that the great majority of patients with spKt/V values above 1.2 had eKt/V levels above 1.05, whereas in those patients who were “misclassified” according to spKt/V , the difference with the eKt/V target was very small.

For calculation of URR only pre- and post-dialytic urea measurements are needed. Therefore, it is a simple and time-saving calculated index^{18,22}. However, weight of the patient, ultrafiltration volume and treatment time is not taking into account in this formula and therefore deviations with the gold standard parameter may be assumed. Especially at higher levels of URR, the discrepancy with Kt/V was found to increase in previous studies^{20,21}. Nevertheless, in the present study, correlation was highly significant, but relationship became exponential for $\text{eKt/V} > 1.3$. Nine % of patients with a URR above **minimum** (65%) had eKt/V below 1.05 (<1.05 but ≥ 0.93). Mean eKt/V in these patients was 0.99.

Differences in dialysis parameters which were related to misclassification when URR is used instead of eKt/V to express target or minimum achieved dose were sex, treatment time and ultrafiltration volume. For the spKt/V formula, treatment time (<10 hours a week) and urea distribution volume were lower in those patients who were above the minimal dose according to spKt/V , but below the minimal dose according to eKt/V . At low urea distribution volumes and short treatment time a larger rebound effect will be expected, which might explain the discrepancy between URR and spKt/V with eKt/V . The relation between misclassification according to URR and ultrafiltration volume can be explained by the notion that convective urea clearance, which is related to ultrafiltration volume, is not taken into account when using URR¹².

In agreement with previous studies^{14-17,19,23,24}, we found that eKt/V , spKt/V , and URR were significantly related to survival. However, when analyzing the minimum cut-off values, only eKt/V below these values predicted mortality significantly, although the trend also suggested better survival with higher URR and spKt/V values. When taking residual renal urea clearance into account, the same predictions at the same cut-off values were observed.

A potential drawback of this study is the observation that a relatively small number of patients had an eKt/V above target, which could be attributed to the presence of residual renal function in a significant percentage of patients. Indeed, taking residual renal function into account, weekly Kt/V could be considered adequate in the majority of patients. Considering that the number of misclassified patients was relatively small, differences in outcome between patients of which adequacy was over-estimated due

to URR- and spKt/V -targets, and patients who were correctly classified could not be assessed significantly.

Concluding, the results of our study show that treatment minimums according to eKt/V are overestimated by cut-off values of spKt/V and URR in respectively 4% and 9% of patients. The disagreement between the different formulas was related to a low urea distribution volume and dialysis treatment time, and, in case of URR, also to ultrafiltration volume.

Although all adequacy parameters were related to mortality, only in case of eKt/V , the cut-off value for minimum achieved dose predicted mortality.

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Appendix Mathematical definitions

1. URR: $1 - \frac{C0 - C_{end}}{C0} \times 100\%$
2. spKt/V: $-LN\left(\left(\frac{C_{end}}{C0}\right) - 0,008 \cdot t\right) + \left(4 - 3,5 \cdot \left(\frac{C_{end}}{C0}\right)\right) \cdot \frac{Uf}{Wt}$
3. eKt/V: $\frac{spKt / V - (0.6 \times spKt / V)}{t} + 0.03$
4. V (Watson):
 males: $2,447 - 0,09516 \cdot A + 0,1074 \cdot Ht + 0,3362 \cdot Wt$
 females: $-2,097 + 0,1069 \cdot Ht + 0,2466 \cdot Wt$
5. rGFR: $\frac{(URE / (C_{end} + C))}{2} \times (1000 / 1440)$
6. rKt/V(wk): $\frac{rGFR \times 1440 \times 7}{V \times 1000}$
7. eKt/V(wk): $eKt / V \times HDfrequency$
8. spKt/V(wk): $spKt / V \times HDfrequency$

C_{end}: Plasma concentration of urea end session (mmol/l)

C₀: Plasma concentration of urea before session (mmol/l)

C: Plasma concentration of urea after interdialytic interval, before next dialysis session (mmol/l)

V: urea distribution volume

URE: urea output in interdialytic urine collection (mmol/d)

t: treatment time(in hours)

A: age

Wt: weight after the haemodialysis session (in kilogram)

Ht: length (in centimeters)

Uf: ultrafiltration (weight before dialysis session minus weight after dialysis session in litres)

rGFR: renal urea clearance (in ml/min)

Chapter 8

Ionic dialysance and the assessment of Kt/V : the influence of different estimates of V on method agreement

Karin Moret, Charles H Beerenhout, A Warmold L van den Wall Bake, Paul G Gerlag, Frank M van der Sande, Karel M Leunissen, Jeroen P Kooman

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Abstract

Background

Ionic dialysance was recently introduced as a means to assess dialysis adequacy (K_{IDt}/V). With this method, urea distribution volume (V) has to be estimated. The primary aim of the present study was to assess the agreement between equilibrated Kt/V assessed by urea kinetic modelling (eKt/V) and K_{IDt}/V taking into account different estimates of V , and to assess the monthly variation in V . Secondly, the mechanisms behind the intra-treatment changes in ionic dialysance and inter-treatment variability of K_{IDt}/V were assessed.

Methods

Sixty-six patients were included. eKt/V was estimated using 30 min post-treatment sampling in the second generation Daugirdas equation. V was assessed by the formulae of Watson and Chertow (V_{Watson} ; V_{Chertow}), double-pool urea kinetic modelling (V_{UKM}) and by ionic dialysance (V_{IOD}) [Diascan; Hospal®].

Results

The use of V_{UKM} or V_{IOD} instead of V_{Watson} or V_{Chertow} improved the relation between eKt/V and K_{IDt}/V (both $r=0.93$; $p<0.001$ vs $r=0.84$ and $r=0.81$; $p<0.001$). Mean values of eKt/V (1.19 ± 0.21), K_{IDt}/V_{UKM} (1.19 ± 0.30) and K_{IDt}/V_{IOD} (1.21 ± 0.25) were comparable.

Intra-class correlation coefficient of V_{IOD} was 0.87 with a 1-month interval and <0.75 after 2 and 3 months. Intra-class correlation coefficient of V_{DP} was 0.79 with a 1-month interval and <0.75 after 2 and 3 months.

Inter-treatment variation in K_{IDt}/V during six consecutive dialysis sessions was $6.1\pm0.6\%$. Changes in blood flow were the main determinant of variations in K_{IDt}/V ($p<0.05$). During treatment, ionic dialysance decreased by 12 ± 13 ml/min ($p<0.001$). The decline in blood volume was the major determinant of the intra-dialytic change in ionic dialysance ($p<0.05$).

Conclusion The use of V_{IOD} and V_{UKM} results in better agreement between eKt/V and K_{IDt}/V compared with anthropometric formulae. K_{IDt}/V was comparable with eKt/V and thus lower than expected for a single-pool method. V_{IOD} and V_{UKM} should be assessed at least monthly. K_{IDt}/V varies widely between consecutive dialysis sessions, mainly due to differences in blood flow. During treatment, ionic dialysance decreases, which is related to the relative decline in blood volume.

Introduction

An adequate delivery of haemodialysis treatment dose is an important factor in the morbidity and mortality of patients treated with haemodialysis¹. Regular evaluation of delivered treatment dose, commonly performed by measurement of Kt/V, is necessary to intervene when the delivered treatment is inadequate.

To assess Kt/V, the second generation Daugirdas formula is advocated by both K-DOQI and EDTA guidelines^{2,3}. Both guidelines recommend measurement of haemodialysis dose at least once a month. Recent studies suggest that substantial variation in delivery of Kt/V occurs within intra-individual haemodialysis treatments on a session-to-session basis^{4,5}. Thus, a more frequent assessment of Kt/V is desirable. However, the need for blood sampling makes more frequent assessment of Kt/V by the standard approach, impractical.

Techniques based on measurement of ionic dialysance facilitate the evaluation of dialysis dose by online monitoring of the Kt/V ($K_{ID}t/V$)⁶⁻⁸. Assessment of dialysis dose based on ionic dialysance was shown to correlate well with Kt/V assessed by traditional urea kinetic modelling^{8,9}. However, despite highly significant correlations, several studies showed either lower or higher values of $K_{ID}t/V$ compared with Kt/V assessed by urea kinetic modelling. One reason for these differences is the fact that in some studies, $K_{ID}t/V$, which is a single-pool model, was compared with equilibrated Kt/V (eKt/V)^{5,8}. However, another factor which is likely to play a major role in the disagreement between $K_{ID}t/V$ and Kt/V assessed by traditional modelling is the estimation of urea distribution volume (V). With the ionic dialysance method, V has to be inserted in order to calculate the final $K_{ID}t/V$. So far, in the studies which addressed $K_{ID}t/V$, most commonly the Watson formula is used to assess V (V_{Watson})⁸. However, several studies questioned the reliability of these anthropometry-based equations^{4,11}. Assessment of V by urea kinetic modelling (V_{UKM}) may be more reliable in this aspect¹⁸. Recently, an estimate of V with the use of ionic dialysance measurements has been proposed (V_{IOD}), which correlated very well with V obtained by direct dialysis quantification and bio-impedance measurements^{12,13}. However, a comparison of V_{IOD} with other estimates of V regarding the agreement between Kt/V, assessed by urea kinetic modelling and $K_{ID}t/V$ was only assessed in one study in 10 patients¹³. Moreover, the frequency by which V_{IOD} or V_{UKM} would have to be assessed is not known.

Two previous studies showed substantial inter-treatment variations in $K_{ID}t/V$ ^{5,14}. Although the mechanisms behind these variations remain partly understood, inter-treatment differences in dialysis time and blood flow rate appear to be major determinants⁵. However, until now, only one study has assessed determinants of inter-treatment variations in $K_{ID}t/V$ ⁵. One recent study also made apparent that ionic dialysance might change during the dialysis therapy¹⁵. Although systemic salt loading due to the conductivity measurements might be partly responsible for this

phenomenon, also a reduction in clearance per se, e.g. due to fouling of the membrane, might lead to a reduction in ionic dialysance. The primary aim of the present study was, firstly, to assess the agreement between $K_{ID}t/V$ with eKt/V taking into account different estimates of V . Secondly, possible mechanisms behind the inter-treatment variability of $K_{ID}t/V$ and intra-treatment changes in ionic dialysance were assessed.

Subjects and methods

Of our HD patient population, we asked all patients who had been on dialysis for more than three months to participate in the present study. Three patients refused to participate. Sixty-six patients were included in the study. No changes were made to the dialysis prescriptions over the study period. The study protocol was approved by the local medical ethical committee and informed consent was obtained from each patient. Patient characteristics are displayed in Table 8.1. In 13 patients, residual renal function was present. Mean GFR in these patients was 2.4 ± 2.6 ml/min. Three patients had a central venous catheter. The others were dialyzed by either forearm or upper arm fistula or PTFE grafts. Three patients were dialyzed two times weekly, the others three times weekly.

Table 8.1 Patient characteristics.

Age (years)	63 ± 17
Male/Female	39 / 27
Weight (kg)	71 ± 11
Length (cm)	168.5 ± 10.9
Dialysis duration (hours)	4 ± 0.5
Time on haemodialysis (months)	37.5 ± 32.8

Study protocol

The agreement between eKt/V and $K_{ID}t/V$ was assessed after the longest dialysis interval. The inter-treatment variation in $K_{ID}t/V$ (using V_{Watson}) was assessed during six consecutive treatments, as was the intra-treatment variation in ionic dialysance. All treatments were monitored for changes in blood flow, relative blood volume, ultrafiltration volume, treatment time, venous pressure, arterial pressure and transmembrane pressure.

Dialysis strategy

All but three patients (as mentioned earlier) were treated three times weekly with haemodialysis, using bicarbonate as buffer and a sodium dialysate concentration of 138 mmol/l. Polysulfone (F8HPS; Fresenius®) dialysis membranes were used. Target blood flow was 300 ml/min, whereas reached blood flow was 275 ± 40 ml/min.

Urea kinetic modeling

Pre- and post-dialysis serum urea samples were taken to measure urea reduction at the dialysis session after the longest interval. Post-dialysis blood samples for assessment of eKt/V were drawn by venipuncture 30 min after the end of dialysis. The eKt/V was estimated using the second generation Daugirdas equation with the 30 min post-dialytic blood samples added in^{2,3}. Also single-pool Kt/V was assessed employing the second generation Daugirdas equation (appendix), using post-dialytic samples drawn 2 min after dialysis.

Ionic dialysance

K_{IDt}/V was measured online by Diascan® (Hospal-Gambro®)^{6,16}. The calculation of the mean ionic dialysance is based on differences in inlet and outlet conductivity values after a conductivity pulse of 1mS/cm every 30 min. Mean ionic dialysance multiplied by the real duration of the session is used to calculate K_{IDt} . K_{IDt} was divided by V_{Watson} , ($V_{Chertow}$), V_{UKM} and V_{IOD} , respectively, to assess agreement with eKt/V.

Determinants of inter-treatment changes in K_{IDt}/V_{Watson} were assessed during six consecutive treatments (n=396).

During the same treatments, determinants of intra-treatment variations in ionic dialysance were assessed.

Urea distribution volume

V was determined using anthropometrically derived V (V_{Watson}), based on the Watson formula, taking into account post-dialysis weight, height, gender and age¹⁷. V was also determined using the Chertow formula¹⁸ (appendix).

In addition, V was assessed based on the formula recently proposed by di Filippo et al. taking into account both plasma urea samples and ionic dialysance measurements (V_{IOD}) (appendix)¹². Post-dialysis blood samples for assessment of V_{IOD} and V_{UKM} were drawn 2 min after the end of dialysis using the slow flow technique¹¹. V_{UKM} was calculated using the calculator available on the HDCN page (<http://www.hdcn.com/calcf/dzer.htm>). This calculator is based on the two-urea sampling approach as described in¹⁹. The single-pool volume is corrected by the programme to a double-pool volume as described in²⁰ (appendix). Variations in V_{IOD} and V_{UKM} were reported during the first dialysis session of the first week of four consecutive months.

Changes in relative blood volume

Changes in relative blood volume are determined by an on-line optical method (Hemoscan®; Hospal-Gambro®), assessing relative blood volume changes from blood hemoglobin concentration changes.

Statistical analysis

The agreement between data was analyzed using Pearson's r and Bland–Altman analysis²¹. Differences between eKt/V and K_{IDt}/V using the different estimates of V were assessed by the student t -test. The standard deviation in K_{IDt}/V and ionic dialysance during the six different treatments were related to the standard deviation of various potential determinants. Multivariate analysis was used to assess determinants of inter-dialytic variation in K_{IDt}/V and intra-treatment changes in ionic dialysance. P values <0.05 were considered significant. The variations in V_{IOD} and V_{UKM} were also assessed using the coefficient of variation and the intra-class correlation coefficient. An intra-class correlation coefficient <0.85 was considered unacceptable for clinical purposes. The SPSS-12.0 package was used for statistical analysis.

Results

Agreement between K_{IDt}/V and eKt/V in relation to different estimates of V

In five patients with inter-dialytic weight gain <0.1 kg, the formula for V_{IOD} yielded unreliable results (NB: in patients with inter-dialytic weight gain >0.3 kg, adequate values for V_{IOD} could be calculated. No patient had inter-dialytic weight gains between 0.1 and 0.3 kg). Therefore, data of 61 patients were analyzed.

The eKt/V was 1.19 ± 0.21 . K_{IDt}/V was 1.12 ± 0.21 when corrected for V_{Watson} ($p < 0.001$ compared with eKt/V) 1.00 ± 0.19 when corrected for $V_{Chertow}$ ($P < 0.001$); 1.19 ± 0.30 when corrected for V_{UKM} ($P = ns$) and 1.21 ± 0.25 ($P = ns$) when corrected for V_{IOD} . Single-pool Kt/V , assessed by urea kinetic modeling, was 1.32 ± 0.31 ($P < 0.001$).

The correlation between K_{IDt}/V and eKt/V was highly significant ($r = 0.84$ and $r = 0.81$; $P < 0.001$), both when using V_{Watson} and $V_{Chertow}$ as an estimate of V , although a significant difference between both methods was observed [0.08 ± 0.13 ; $P < 0.05$] and [0.20 ± 0.13] with wide limits of agreement (Figure 8.1). Both when using V_{UKM} and V_{IOD} as estimates of V , the correlation between K_{IDt}/V and eKt/V became stronger (both $r = 0.93$ $P < 0.001$) and limits of agreement were narrower [0.00 ± 0.09] and [-0.01 ± 0.14] (Figures 8.2 and 8.3).

Figure 8.1 Agreement between eKt/V and $K_{ID}t/V$ using V_{Watson} as estimate of V . eKt/V : Double-pool Kt/V according to second generation Daugirdas formula; $K_{ID}t/V$: Kt/V assessed by ionic dialysance.

Figure 8.2 Agreement between eKt/V and $K_{ID}t/V$ using V_{UKM} as estimate of V . V_{UKM} : Urea distribution volume assessed by double-pool urea kinetic modelling.

Figure 8.3 Agreement between eKt/V and $K_{ID}t/V$ using V_{IOD} as estimate of V . V_{IOD} : Urea distribution volume assessed by double-pool urea kinetic modelling with use of ionic dialysance.

Monthly variation of V_{IOD} and V_{UKM}

Coefficient of variation of V_{IOD} was 15.7% when V_{IOD} measurements were compared with a one-month interval, 19.7% when V_{IOD} was compared with a two-month, and 15.7% when V_{IOD} was compared with a three-month interval.

Intra-class correlation coefficient of V_{IOD} was 0.87 when V_{IOD} measurements were compared with a one-month interval, 0.68 when V_{IOD} was compared with a two-month, and 0.74 when V_{IOD} was compared with a three-monthly interval.

Coefficient of variation of V_{UKM} was 9.5% when V_{UKM} measurements were compared with a one-month interval, 16% when V_{UKM} was compared with a two-monthly, and 11.7% when V_{UKM} was compared with a three-monthly interval.

Intra-class correlation coefficient of V_{UKM} varied from 0.79, 0.73 and 0.57, respectively with a one-, two- and three-monthly interval.

Inter-treatment variation in $K_{ID}t/V$ and intra-treatment variation in ionic dialysance

Three hundred and ninety-six sessions were studied. Mean coefficient of variation of $K_{ID}t/V$ between the six measurements was $6.1 \pm 4.1\%$ (range 1.3–21.5%). The inter-treatment variation in $K_{ID}t/V$ is displayed in Figure 8.4.

With multivariate analysis, the variation in blood flow appeared to be the independent parameter explaining the variation in $K_{ID}t/V$ (Table 8.2).

Mean ionic dialysance at the start of dialysance was 170 ± 17 ml/min.

During treatment, ionic dialysance declined by a mean of 11.8 ± 8.9 ml/min ($P < 0.001$). With multivariate analysis, the intra-treatment change in ionic dialysance was significantly related to the decline in relative blood volume and blood flow rate (Table 8.3).

Figure 8.4 Inter-treatment variation in $K_{\text{id}}t/V$ during six consecutive haemodialysis sessions. V_{Watson} : Urea distribution volume assessed by anthropometry (Watson formula).

Table 8.2 Multivariate analysis of determinants for inter-treatment variation in Kt/V_{id} .

	β	05% CI	<i>P</i>
Venous pressure	0.24	[0.00-0.002]	0.06
Ultrafiltration volume	-0.19	[-0.038 to 0.014]	ns
Blood flow	0.30	[0.00-0.002]	0.016
Dialysis time	0.13	[0.011 to 0.043]	ns
Decline in blood volume	0.15	[0.006 to 0.022]	ns

Table 8.3 Multivariate analysis of determinants for intra-treatment variation in ionic dialysance.

	β	05% CI	<i>P</i>
Venous pressure	-0.17	[-0.28 to 0.05]	ns
Ultrafiltration volume	0.09	[-4.08 to 8.1]	ns
Blood flow	0.15	[-0.06 to 0.23]	ns
Dialysis time	0.14	[-1.3 to 5.7]	ns
Decline in blood volume	0.39	[0.85 - 4.60]	0.005

Discussion

Our study confirms previous findings^{5,6,8–11,22,23} of a good correlation between K_{IDt}/V and Kt/V assessed by urea kinetic modelling, but showed significant differences between both methods when anthropometric formulae were used to estimate V . Compared with our study, McIntyre et al. showed a better agreement between K_{IDt}/V and eKt/V with V_{Watson} as an estimate of V , but studied a more homogeneous group of patients. We studied an unselected group of dialysis patients, nearly comprising the entire haemodialysis population of a single centre. Recent studies questioned the reliability of the anthropometry-based equations and suggested that assessment of V assessed by urea kinetic modelling might be more reliable in this aspect^{4,12}.

When using V_{UKM} or V_{IOD} in the present study, the relation between eKt/V and K_{IDt}/V improved. Mean values of eKt/V and K_{IDt}/V were nearly comparable, despite the fact that K_{IDt}/V is calculated according to a single-pool model. This is in agreement with the results of McIntyre et al. who also showed comparable values between eKt/V and K_{IDt}/V , but in contrast to the data of Filippo et al. who showed higher values for K_{IDt}/V compared with eKt/V , and to the study of Wuepper et al. where K_{IDt}/V was comparable with single-pool Kt/V ^{5,12,13}. It has been postulated that ionic dialysance may underestimate effective urea clearance due to the effects of systemic salt loading during the ionic dialysance measurements, resulting in a reduced conductivity diffusion gradient across the dialyser, especially when urea clearance is >150 ml/min¹⁵. This might explain the fact that K_{IDt}/V , both in our study and in the study of McIntyre, was lower than expected for a single-pool model⁵. However, in chapter 6, we found no evidence for systemic sodium loading during ionic dialysance measurements when assessed during an entire dialysis session. However, possible effects on short-term variations can not be refuted. Differences between the results obtained by Filippo et al. on one hand, and McIntyre and our study on the other hand, could theoretically be explained by lower levels of urea clearance in the former study^{5,12}. However, this is unlikely in view of the fact that ionic dialysance in patients studied by Filippo was comparable with our patients¹². In contrast to most other studies, Wuepper et al. used a model based on a two-step change in conductivity, which has different effects on systemic changes in sodium^{13,15}.

However, even with a two-step change in conductivity, ionic dialysance may underestimate urea removal²³, which may be related to the effects of cardiopulmonary recirculation²⁴.

V_{IOD} , calculated according to single-pool kinetics, yielded comparable data to V_{UKM} , calculated according to double-pool kinetics. This is in agreement with the data of Filippo who showed comparable results between V assessed by direct dialysis quantification (a double pool V) and V_{IOD} ¹². It has been shown that with haemodialysis with conventional dose prescriptions the ratio between V assessed by single-pool and double-pool kinetics is nearly one to one²⁵. A drawback of our study is the fact that we

did not calculate V according to direct dialysis quantification or bio-impedance analysis.

In the small proportion of patients with inter-dialytic weight gain <0.1 kg, calculation of V_{IOD} yielded unreliable values, which may possibly be due to the fact that V_{IOD} was calculated according to single pool variable volume kinetics.

If V is to be assessed by V_{IOD} or V_{UKM} , the question arises how often V should be measured. Kloppenburg et al. showed relatively large intra-patient variability in V assessed by urea kinetic modelling⁴. From the data in the present study, the variability in V_{IOD} or V_{UKM} during a one-month period would appear acceptable for clinical purposes, but not when measurements of V are performed with longer time intervals. In agreement with earlier data of Lambie et al.¹⁴, a significant inter-treatment variation in K_{IDt}/V was observed. In our study, this variation appeared to be mainly related to variations in blood flow rate. Although blood flow rate is routinely prescribed as 300 ml/min in our centre, sometimes the blood flow rate had to be decreased in response to changes in venous or arterial pressure, among other reasons, due to needle malpositions. The variations in blood flow rate between treatments are in agreement with the study of Lambie et al.¹⁴. In our study, changes in treatment time played less of a role compared with the findings of Stewart et al. because treatment time was basically kept unchanged.

In the present study, a decline in ionic dialysance during the dialysis session was observed, which also was described by Gotch et al.¹⁵. The change in ionic dialysance was related to the change in relative blood volume. The mechanism behind this phenomenon remains to be determined. However, it may be hypothesized that increased clotting of proteins to the dialyser membrane might be involved in less diffusive capacities. In addition, also systemic salt loading due to the conductivity measurements per se might affect measurements of ionic dialysance during dialysis¹⁵. This phenomenon is especially relevant above a urea clearance of 150 ml/min¹⁵ and therefore may also have played a role in the measured changes in the present study. Also, due to the hemoconcentration, the blood water flow rate decreases, resulting in a decline in urea clearance and ionic dialysance during the session.

Concluding, K_{IDt}/V is a useful tool to assess dialysis dose. The use of V_{IOD} and V_{UKM} result in better agreement between eKt/V and K_{IDt}/V compared with anthropometric formulae. K_{IDt}/V was comparable with eKt/V , and thus, lower than expected for a single-pool method. Due to the variability in V_{IOD} and V_{UKM} these parameters should be assessed at least monthly. K_{IDt}/V varies widely between consecutive dialysis sessions, mainly due to differences in blood flow. During treatment, ionic dialysance decreases, which is related to the relative decline in blood volume.

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Glossary of terms

α :	rate of interdialytic weight gain (ml/min)
A:	age (years)
C0:	initial plasma water urea concentration (mmol/l)
C _{end} :	end-dialysis plasma water urea concentrations determined in blood samples taken at the end of the session with the blood pump speed reduced to 50mL/min for two minutes (mmol/l)
C _{end+30} :	end-dialysis plasma water urea concentrations determined in blood samples taken 30 minutes after the end of the session (mmol/l)
C _{next} :	plasma water urea concentration before the start of the subsequent dialytic treatment (mmol/l)
eKt/V:	double-pool (equilibrated) Kt/V according to the second generation Daugirdas formula
spKt/V:	single-pool Kt/V according to the second generation Daugirdas formula
GFR:	glomerular filtration rate
G:	urea generation rate (mg/min)
Ht:	height (cm)
ID:	ionic dialysance (mL/min)
K:	dialyser clearance
K _{ID} t/V:	Kt/V according to ionic dialysance
K _{ID} t/V _{chertow} :	Kt/V according to ionic dialysance, with urea distribution volume assessed by the Chertow formula
K _{ID} t/V _{IOD} :	Kt/V according to ionic dialysance, with urea distribution volume assessed by single-pool urea kinetic modeling with use of ionic dialysance
K _{ID} t/V _{UKM} :	Kt/V according to ionic dialysance, with urea distribution volume assessed by double-pool urea kinetic modeling
K _{ID} t/V _{watson} :	Kt/V according to ionic dialysance, with urea distribution volume assessed by the Watson formula
Qf:	rate of ultrafiltration (ml/min)
t:	duration of treatment time (min)
Ti:	interdialytic interval (min)
Uf:	ultrafiltration (ml)
URR:	urea reduction rate
V:	urea distribution volume
V _{chertow} :	urea distribution volume calculated by the Chertow formula
V _{UKM} :	urea distribution volume calculated by urea kinetic modeling
V _{IOD} :	urea distribution volume calculated by single-pool urea kinetic modeling with use of ionic dialysance

V_{watson} :	urea distribution volume calculated by the Watson formula
V_{sp} :	effective urea distribution volume given by the single pool model
Wt:	postdialysis weight (kg)
Wp:	predialysis weight (kg)

Appendix Mathematical definitions

1. URR:

$$1 - \frac{C0 - C_{end}}{C0} \times 100\%$$

2. spKt/V:

$$-\ln\left(\left(\frac{C_{end}}{C0}\right) - 0,008 \cdot t\right) + \left(4 - 3,5 \cdot \left(\frac{C_{end}}{C0}\right)\right) \cdot \frac{Uf}{Wt}$$

3. eKt/V:

$$\frac{spKt/V - (0.6 \times spKt/V)}{t} + 0.03$$

4. V (Watson):

$$\text{males:} \quad 2,447 - 0,09516 \cdot A + 0,1074 \cdot Ht + 0,3362 \cdot Wt$$

$$\text{females:} \quad -2,097 + 0,1069 \cdot Ht + 0,2466 \cdot Wt$$

5. V (IOD):

$$(Q_f \cdot t) \cdot \left[\left[1 - \left(\frac{G - C_{end} \cdot (ID - Q_f)}{G - C0 \cdot (ID - Q_f)} \right)^{\frac{Q_f}{(ID - Q_f)}} \right]^{-1} - 1 \right]$$

where

G(mg/min):

$$G = \alpha \cdot \frac{C_{next} - C_{end} \cdot \left(\frac{V + \alpha \cdot Ti}{V} \right)^{-1}}{1 - \left(\frac{V + \alpha \cdot Ti}{V} \right)^{-1}}$$

6. V (Chertow):

$$\begin{aligned} & -0.0749 \cdot A - 1.0178 \cdot male + 0.127 \cdot Ht - 0.0401 \cdot Wp + 0.579 \cdot \\ & diabetes - 0.000672 \cdot Wp^2 - 0.0349 \cdot (A \cdot male) + 0.1126 \cdot \\ & (male \cdot Wp) + 0.00104 \cdot (A \cdot Wp) + 0.00186 \cdot (Ht \cdot Wp) \end{aligned}$$

where

male is equal to 1 for males and 0 for females and
diabetes is 1 for diabetics and 0 for nondiabetics

7. V (UKM):

$$\frac{FKt}{LN \frac{FC0}{C_{end}}}$$

where

$$F: \quad 1 - 0.44 \frac{K}{V_{SP}}$$

and

$$V_{SP}: \quad \frac{Kt}{\ln \left(\frac{C0}{C_{end}} \right)}$$

8. rGFR:

$$\frac{(URE / (C_{end} + C))}{2} \times (1000 / 1440)$$

9. rKt/V(wk):

$$\frac{rGFR \times 1440 \times 7}{V \times 1000}$$

10. eKt/V(wk):

$$eKt / V \times HDfrequency$$

11. spKt/V(wk):

$$spKt / V \times HDfrequency$$

Chapter 9

Summary and discussion

Summary and discussion

This thesis comprises two parts: the first part focuses on different aspects concerning the regulation of sodium balance during dialysis. These aspects were studied both during routinely described hemodialysis as well as during different modifications, such as feedback technologies and sodium profiles.

The second part focuses on the monitoring of dialysis efficacy. This was studied by conventional urea kinetic modeling and by the ionic dialysance method.

First Part

Validation of plasma conductivity and ionic mass balance measurements

In this thesis, plasma conductivity and ionic mass balance were used as a surrogate of respectively plasma sodium and sodium balance during dialysis.

The main advantages of plasma conductivity and ionic mass balance is that both can be studied without the need for blood sampling and are, with dedicated technology (Diascan®; Hospal-Gambro), available during every dialysis treatment*:

* in this thesis, for sake of simplicity and in agreement with terminology in the literature, the term plasma conductivity is used, whereas the Diascan® device actually calculates conductivity in plasma water

As described in detail in Introduction of the thesis, conductivity of a solution is the ability to conduct an electrical current. Plasma conductivity is assessed by a simple mathematical formula which includes ionic dialysance and changes in outlet dialysate conductivity after a temporary increase in dialysate conductivity at the dialyzer inlet:

Earlier studies showed a near linear relation between plasma sodium and plasma conductivity. In these studies, plasma conductivity measured in mS/cm was found to be ± 2 mmol/l lower as compared to plasma sodium measurements, in accordance to the formula:

Plasma sodium = (Plasma conductivity $\times 10.4$) - 9.57¹. Based on results of different studies, plasma conductivity appears to be adequately validated as surrogate parameter of plasma sodium. Nevertheless it has to be considered that also other ions, although in a lesser degree, may influence plasma conductivity.

This affects also the relation between dialysate conductivity and dialysate sodium, as total conductivity can be influenced by other ions such as chloride and bicarbonate, which may change throughout the dialysis treatment. Although this was not described in full detail in **chapters 3 and 4**, with a dialysate conductivity prescription of 14.0 mS/cm, dialysate sodium measurements by flame photometry and indirect ionometry were comparable (140.4 ± 1.5 and 139.9 ± 0.7 mmol/l), but lower when assessed by direct ionometry (135.4 ± 1.1 mmol/l). As described in Introduction, this is likely due to formation of a complex with sodium and other ions in the dialysate, which is not measured by direct ionometry. Therefore, in agreement with la Milia³, the estimate of sodium removal in total dialysate collections is dependent on the methodology used, with indirect ionometry and flame photometry likely being the preferred approach.

As for the use of ionic mass balance (IMB) measurements as a surrogate for sodium balance, fewer validation data were available in the literature. Using a formula based on changes in plasma sodium during dialysis and ultrafiltration volume, Lambie observed a significant correlation between sodium balance assessed by this method and ionic mass balance measurements². In **chapter 4**, ionic mass balance was

validated against sodium balance by dialysate collections (in which sodium was measured by flame photometry) and compared with the counted ions by the dialysis machine (Diascan®). Also, in this study, a very strong relation was observed between sodium balance and ionic mass balance [$r^2=0.95$], although in individual patients, some discrepancies between both methods were observed. Whether these are due to the inherent variation in sodium measurements, or to changes in other ions in dialysate during the course of dialysis treatment cannot be deduced from this study. In **chapter 5**, ionic mass balance measurements by Diascan® were shown to correlate highly significantly with conductivity measurements in dialysate collections.

Summarizing, with the limitations discussed above kept in mind, ionic mass balance measurements as a surrogate for sodium balance, plasma conductivity as a surrogate for plasma sodium and dialysate conductivity as a surrogate for dialysate sodium, were used in the remainder of the thesis.

Relation between plasma conductivity and ionic mass balance

Sodium balance during dialysis is mainly based on convection. However, also diffusion, due to a difference in plasma and dialysate sodium may play an important role. This was clearly shown in **chapter 3 and 4**, in which a very strong relation between pre-dialytic plasma conductivity and diffusive ionic mass balance was observed. Both in a controlled study during isovolemic dialysis, and in a facility database in which treatments of all patients over a period of 6 months were analyzed.

In the study with isovolemic dialysis reported in **chapter 3**, which included 13 patients, ionic mass transfer from dialysate to patient was observed when plasma conductivity was 0.2-0.3 mS/cm lower than dialysate conductivity, or when plasma sodium was 2 mmol lower than dialysate sodium. In basic agreement, in the database study reported in **chapter 4**, diffusive ionic influx appeared to occur when pre-dialytic PC was below 14.25 mS/cm (roughly corresponding to a plasma sodium concentration of 139 mmol/l) when a dialysate sodium of 140 mmol/l was prescribed. The explanation for the discrepancies between both studies is not entirely clear. However, due to the effects of ultrafiltration, protein coating of the dialyzer membrane might influence the Donnan effect, and therefore diffusive ionic mass balance. In addition, also pH changes during dialysis may interfere with the Donnan effect^{4,5}.

In the study reported in **chapter 4**, diffusive mass balance accounted for 18.3±16.7% of total mass balance. However, the large range [0.4 - 75.3%] shows that in individual patients, diffusive mass balance may contribute significantly to total IMB.

Several other studies also assessed the effects of dialysate sodium on sodium balance during dialysis. In the study of Song, diffusive sodium influx appeared to occur at dialysate sodium levels from 137.8 mmol/l⁶, whereas Flanigan observed an inter-dialytic increase in plasma sodium in a significant subset of patients when treated

with a dialysate sodium concentration of 140 mmol/l⁷. Whether the (minor) differences between studies can be attributed to differences in dialyzer membrane characteristics (e.g. according to protein adsorption) or ultrafiltration rate is not definitely established.

Summarizing, the exact pre-dialytic plasma sodium concentration at which an inward direct diffusive transport occurs, cannot be definitely identified from the thesis, and is also likely dependent on dialysis-related factors such as ultrafiltration. According to the results reported in **chapter 4**, zero diffusive mass balance would be expected when dialysate sodium concentration approximates plasma sodium concentration.

An important extrapolation from **chapter 3 and 4**, and from studies of others, is that with frequently applied sodium concentrations of the dialysate (140 mmol/l), in patients with low pre-dialytic plasma sodium levels, diffusive influx of sodium from the dialysate to the patient may occur. Indeed, although ionic mass removal from patient to dialysate was observed in nearly all treatments, in nearly 33% of patients studied in **chapter 4**, diffusive ionic mass transfer from dialysate to patient and a rise in plasma conductivity was observed. From data in the literature, in general, a dialysate sodium concentration of around 137-138 mmol/l would appear to provide a reasonable balance between the prevention of inward diffusive sodium mass transfer and untoward effects of too low dialysate sodium levels on blood volume preservation^{8,9}. For instance, lowering of dialysate sodium from 141 to 138 mmol/l at a facility level resulted in a small improvement in BP control without an increase in hypotensive episodes⁸. In an audit of 2187 patients, the prescription of a dialysate sodium concentration of 140 mmol/l or higher was associated with higher inter-dialytic weight gains, pulse pressure, and even with a higher percentage of intra-dialytic hypotension as compared to patients whom were prescribed a dialysate sodium concentration of 136 or 137 mmol/l⁹.

Whether particularly patients with low pre-dialytic sodium levels and patients with difficult to-treat hypertension would benefit from further lowering of dialysate sodium (e.g. to 136 mmol/l) is an interesting subject for future studies. In a recent trial, based on tolerability of the participating patients, a reduction of dialysate conductivity of up to 13.0 mS/cm was achieved in some patients, with beneficial effects on hypertension control or inter-dialytic weight gain. Notably, patients with frequent intra-dialytic hypotensive episodes were not included in the trial².

Effects of modification of dialysis treatment on sodium balance and plasma conductivity

Higher dialysate sodium concentrations and/or sodium profiles are frequently used as a method to prevent intra-dialytic hypotension¹⁰. The rationale behind the use of sodium profiles and increased dialysate sodium concentrations is the improvement of

refill of blood volume from the interstitial tissues during ultrafiltration. However, the effect on sodium balance has not been widely studied.

Based on the results of **chapter 3**, ionic mass balance is well able to distinguish between treatments which differ in dialysate sodium prescription. Ionic mass removal was significantly lower in patients treated with a supraphysiologic dialysate sodium concentration of 144 mmol/l [80 mmol] as compared with a dialysate sodium concentration of 140 mmol/l. In the study described in **chapter 5**, in which different maneuvers used to prevent intra-dialytic hypotension were compared (including sodium profiling), each during 11 consecutive treatments, difference in ionic mass balance was observed during the first treatment only, whereas pre-dialytic plasma conductivity increased during the period in which the sodium profile was prescribed. Thus, the absence of a lasting effect on ionic mass balance during sodium profiling is likely due to the strong relation between ionic mass balance and pre-dialytic plasma conductivity. During treatment with the sodium profile, due to the increase in pre-dialytic plasma conductivity, the ratio between the dialysate conductivity and pre-dialytic plasma conductivity remained unchanged. These results are in agreement with those of Lambie et al, in which a gradual reduction in dialysate conductivity resulted in a change in ionic mass balance mainly during the first session with the new dialysis prescription².

The increase in plasma conductivity is in some conflict with the paradigm of a pre-set individual plasma sodium setpoint^{4,7,11,12}. According to this paradigm, sodium loading will lead to an increase in thirst and water intake, counteracting the effect of sodium loading on plasma sodium levels. In agreement with data from Thein⁸ but in disagreement with data from others^{2,6,12}, changes in dialysate sodium prescription resulted in changes in plasma conductivity (and thus plasma sodium levels) but not in changes in inter-dialytic weight gain. Whether the lack of a change in inter-dialytic weight gain during the sodium profile in our study occurred at the expense at increased thirst cannot be deduced from the data.

Given the data in the literature, which show that sodium profiles may be associated with increased inter-dialytic weight, hypertension, as well as the effects on plasma conductivity observed in **chapter 5** do not support the use of sodium profiles with supraphysiologic sodium concentrations as a preventive measure for intra-dialytic hypotension. Interestingly, although the number of included patients was small, in **chapter 5**, blood volume controlled feedback appeared to be an effective maneuver in the prevention of intra-dialytic hypotension without untoward effects on sodium balance. Blood volume controlled feedback is a concept at which ultrafiltration rate is adapted based on changes in relative blood volume in order to prevent dialysis hypotension. The efficacy of blood volume controlled feedback is in agreement with earlier studies from the literature, also from our own unit^{13,14}.

Also no difference on sodium balance was observed during plasma conductivity controlled feedback compared to standard dialysis. Plasma conductivity controlled feedback is a technology at which dialysate conductivity is adapted based on online measured plasma conductivity to reach a pre-set end-dialysis plasma conductivity goal. In this study, in agreement with the available literature at that time, we aimed for a post-dialytic plasma sodium concentration^{15,16,17} of 14.0 mS/cm was chosen as target (likely corresponding to a plasma sodium concentration of ± 138 mmol/l). However, in some patients with low-predialytic plasma sodium concentrations diffusive sodium influx might have occurred. Thus, especially in those patients with lower plasma sodium levels, individualization of dialysate sodium would appear an attractive option.

Individualization of dialysate sodium

Data on individualization of dialysate sodium in the literature are scarce. In the study described in **chapter 3**, individualization of dialysate sodium resulted in an increase in sodium removal in those patients with low pre-dialytic PC level, but actually in a reduction in ionic mass removal in those patients with higher pre-dialytic PC. Therefore, at least from theoretical premises, especially those patients with low pre-dialytic plasma sodium levels patients might benefit from individualized sodium prescription. Data in the literature regarding individualized dialysate sodium concentrations are scarce. In the study of de Paula¹⁸, individualization of dialysate sodium by manually setting dialysate sodium to equal patient pre-dialysis plasma water sodium concentration, with a correction factor for the Donnan effect, resulted in an improvement in hypertension control and a decrease in inter-dialytic weight gain. At the same time the incidence of intra-dialytic hypotension reduced according to treatments with a fixed dialysate sodium concentration of 138 mmol/l. In this study, especially those patients with difficult-to-treat hypertension benefited from the lowering of dialysate sodium. Pre-dialytic plasma sodium concentrations before the intervention were already quite low (134.0 ± 1.4 mmol/l), which was due to the fact that patients who had equal or higher plasma sodium concentrations were excluded from the study. A similar approach was followed by Sayarlioglu¹⁹, in which pre-dialytic blood pressure and inter-dialytic weight gain decreased if dialysate sodium was individualized in patients with pre-dialytic plasma sodium concentrations below the standard dialysis sodium concentration. Notably, in all these studies, only stable dialysis patients without frequent intra-dialytic hypotensive episodes were included. Thus, although more research is needed, individualization of dialysate sodium to pre-dialytic plasma sodium concentration appears a promising tool, especially in those patients with low pre-dialytic plasma sodium levels, high inter-dialytic weight gains, and suboptimal hypertension control. However, for individualization of plasma sodium, also more information on variations in pre-dialytic plasma sodium (or plasma

conductivity) would be interesting, given the controversial data in the literature on the presence of a fixed osmolar setpoint in dialysis patients.

Variations in pre-dialytic PC

In order to explore the concept of individual variations in pre-dialytic plasma conductivity, in **chapter 4** a retrospective analysis of all treatments in the facility (4070 measurements in 73 patients) was performed during a period of 6 months, using plasma conductivity as a surrogate for plasma sodium. In this study, the mean coefficient of variation for pre-dialytic PC was 1.3%. Still, the mean intra-individual difference between the lowest and highest pre-dialytic PC measurements during the 6 months follow-up period was ± 0.9 mS/cm [$\sim$ plasma sodium 9 mmol/l]. Interestingly, both inter- as well as intra-variations in pre-dialytic plasma conductivity were related to variations in pre-dialytic blood pressure, which might be a circumstantial argument for volume-independent effects of sodium on blood pressure. Clearly, more research is needed in this area.

Despite the fact that mean intra-patient variations as a whole were relatively minor, the results of the studies in **chapter 4** and **chapter 5** cast some doubt on the existence of a fixed osmolar setpoint in all patients. For individualization of treatment, frequent assessment of plasma sodium or plasma conductivity would appear a reasonable strategy. The on-line availability of plasma conductivity would appear to be a very practical tool to achieve individualization of dialysate sodium prescription without the need for blood sampling. This should be the focus of future studies.

Second Part

Assessment of dialysis adequacy by urea kinetic modeling: is there a preferred method?

Kt/V_{urea} is widely used to assess dialysis adequacy. The output of this formula results in a number, which determines how many times V (estimated urea distribution volume per individual dialysis patient) has to be purified of urea (and other small solutes) during the time of dialysis. In the assessment of dialysis adequacy, there is a discrepancy between the most influential guidelines on this topic, i.e. the European Best Practice Guidelines (EBPG) and Kidney Disease Outcomes Quality Initiative (K-DOQI), regarding the assessment of Kt/V . Whereas K-DOQI recommends the use of $spKt/V$ measurements, EBPG endorses the use of eKt/V , which corrects for urea rebound due to urea compartmentalization after dialysis^{20,21}. Notably, eKt/V is a mathematical correction of $spKt/V$ for which no additional blood sampling is needed. Both guidelines advice to use the urea reduction rate (URR) only as an additional tool in the assessment of dialysis adequacy.

It is not well known to which extent patients would be classified as receiving either an adequate or inadequate treatment when treatment is prescribed according to these different adequacy parameters. It is also not known whether the achievement of treatment targets between the different adequacy parameter has different prognostic power. In **chapter 7**, these questions were addressed in 830 patients of the NECOSAD database. eKt/V above 1.2, a spKt/V above 1.4 and URR above 70% were used as targets for dialysis adequacy, and respectively 1.0, 1.2 and 65% as minimum levels.

Only 5% of patients with spKt/V above 1.4 had an eKt/V below 1.2. In these “misclassified” patients, the mean eKt/V was 1.19, so very close to the treatment target. The percentage “misclassified” patients was somewhat higher when a URR >70% was used as parameter for treatment targets. More or less the same percentage “misclassified” patients was observed when the minimum levels for dialysis adequacy were compared. In survival analysis, an eKt/V , spKt/V and URR below the minimum levels were all associated with a higher risk of mortality, which provides support for the clinical usefulness of these adequacy parameters in dialysis monitoring.

Concluding, from the results in **chapter 7**, the use of either spKt/V or eKt/V is not likely to have a major effect on the prescription of dialysis therapy, under the condition that appropriate cut-off levels are used. The risk of “misclassification” appears to be somewhat enhanced with the use of urea reduction rate as a parameter for dialysis adequacy. Whether this carries the risk of inferior patient outcomes cannot be deduced from this thesis.

Assessment of dialysis adequacy by ionic dialysance

For Kt/V measurements by urea kinetic modeling, blood sampling is needed. As described in the introduction of the thesis, Kt/V assessment by ionic dialysance is a non-invasive method which allows to assess dialysis adequacy on a treatment-to-treatment basis without the need for blood sampling. This is of special importance given the variety in intra-patient Kt/V between treatments observed in **chapter 8** and confirming the results of others²². Although dialysance (the diffusive transfer of a solute through the membrane) and clearance (the depuration of a solution from a given substance) are strictu sensu different concepts, ionic dialysance can be used to assess urea clearance during hemodialysis²³.

In short, ionic dialysance is expected to be comparable to urea clearance based on the similar characteristics of transfer through the dialyser and the osmotic distribution volumes in the blood. As can be seen in the figure below, ionic dialysance (by Diascan®) is measured by assessing changes in dialysate conductivity at the dialyser outlet after a change in inlet dialysate conductivity. The change in outlet conductivity can be used to calculate ionic dialysance, assuming that plasma conductivity does not change during the measurement²⁴. A very strong relation between ionic dialysance

and urea clearance has been observed. However, there appears to be a small underestimation of urea clearance by ionic dialysance, which may affect the relation between Kt/V by urea kinetic modeling and ionic dialysance, as will be discussed below^{24,25}.

Figure 9.1 Scheme of the record of the inlet and outlet dialysate conductivity during a measurement of ionic dialysance where X_1 and X_2 are the two given values of inlet dialysate conductivity, Y_1 and Y_2 the two measured values of outlet dialysate conductivity and C_p the representation of the patient's plasma conductivity. Q_D is dialysateflow, Q_F ultrafiltration rate

Agreement between ionic dialysance and urea kinetic modeling in the assessment of Kt/V

Although Kt/V by ionic dialysance is a single pool method, both in the study described in **chapter 8** and in various studies in the literature, Kt/V by ionic dialysance, when assessed by the Diascan® method, appears to be generally lower as compared to $spKt/V$ by urea kinetic modelling²⁴.

Besides this (small) underestimation of urea clearance by ionic dialysance, this is amongst others due to the method used to estimate urea distribution volume (V), as will be discussed in the following paragraph. The result has to be added in the

calculation of Kt/V by ionic dialysance, in order that V gets a substantial influence on the final result. As the Watson formula, which is the most frequently used anthropometric formula, tends to overestimate urea distribution volume, this would result in a too low estimate of Kt/V . However, Kt/V measured by Diascan® (a single pool method) showed better agreement with eKt/V as compared to $spKt/V$, even when this was calculated by V by urea kinetic modeling (**chapter 8**). The good agreement between eKt/V and Kt/V by Diascan® is in agreement with the study of McIntyre et al.²⁶.

Another factor which may be responsible for the lower estimate of Kt/V by ionic dialysance as compared to urea kinetic modeling could be the effect of cardiopulmonary recirculation. Cardiopulmonary recirculation refers to the fact that part of the blood volume, which flows back from the arteriovenous fistula or graft to the heart is directly returned to the arterial part of the access without passing tissues. This phenomenon is inherently present during dialysis with an arteriovenous access but absent during dialysis with a central venous catheter.

Additionally, the underestimate of Kt/V by ionic dialysance could be explained by the effect of the conductivity pulses on plasma conductivity. For calculation of ionic dialysance, it is assumed that plasma conductivity remains unaffected by the conductivity pulse itself. The stability of the plasma conductivity levels during ionic dialysance measurements has been questioned by Gotch, who hypothesized that the conductivity pulses may result in sodium loading and thus in an increase in plasma conductivity²⁸. In **chapter 6**, the effect of conductivity pulses on ionic mass balance in patients treated with isovolemic dialysis was assessed. No difference in IMB was observed between treatments with and without Diascan® measurements. This is certainly no definite proof for the absence of a temporary effect of conductivity pulses on plasma conductivity. However, the findings of Mercadal discussed above argue for a more important role of cardiopulmonary recirculation in the disagreement between urea clearance and ionic dialysance²⁷.

Interestingly, there appears to be a difference between the two most commonly used methods, i.e. the OCM monitor by Fresenius and Diascan by Gambro in the Kt/V ²⁹. Both methods have slightly different ways to deliver conductivity pulses. The Diascan method delivers a conductivity step of 1 mS/cm during a short time period, with a correction needed for the fact that outlet dialysate conductivity is not completely stabilized during this short time period, whereas the OCM monitor uses a triphasic approach with longer equilibration time²⁴. Whether these methodological differences explain the difference between both methods deserves further investigation.

Urea distribution volume

Differences between ionic dialysance and formal urea kinetic modeling are also dependent on the method used for the determination of urea distribution volume in the denominator. Next to the effects of cardiopulmonary recirculation on the assessment of ionic dialysance discussed above, another reason for the underestimation of spKt/V by ionic dialysance is the fact that the most commonly used *anthropometric formulas* (e.g. Watson) overestimate urea distribution volume (V) as compared to urea kinetic modeling.

The lower urea distribution volume by urea kinetic modeling as compared to anthropometric formula can be explained either by the fact that anthropometric formula do not adequately reflect total body water in dialysis patients, e.g. by the reduction in skeletal muscle mass and a relative increase in visceral fat distribution in dialysis patients³⁰. On the other hand, also a functional redistribution of the urea pool to central compartments, due to a reduction in perfusion of the peripheral compartments during dialysis might contribute to the overestimation of the effective urea distribution volume as compared to anthropometric formula.

As shown in **chapter 8**, and in agreement with data from di Filippo³¹, the use of *kinetic modeling* to calculate urea distribution volume resulted in an improved relation between Kt/V assessed by ionic dialysance and by blood sampling methods. However, the calculation of urea distribution volume by kinetic models is relatively complex for busy clinical practice, even with the use of internet-based calculations, and there is need for blood sampling. This complexity especially appears to hold true if urea distribution volume is calculated by the *ionic dialysance formula*. Moreover, this formula did not appear to be reliable in patients with significant residual renal function, whereas urea distribution volume estimates by *kinetic modeling* and by *ionic dialysance formula* can also be unreliable in case of access recirculation

Therefore, the question remains whether other methods which are easy to apply in the clinic, could not aid in the estimate of the correct urea distribution volume. Bioimpedance, by which total body water is assessed by the impedance of the body to an alternating current, is easy to apply and non-invasive. In a recent study, Lindley et al. found, in agreement to the data in **chapter 8**, an underestimation of dialysis dose if *anthropometric formula* were used, whereas the use of bioimpedance resulted in comparable Kt/V results as compared to calculation of urea distribution volume by *kinetic modeling*³². Also, in a preliminary study performed in our unit, V by the new bioimpedance method BCM® (Fresenius) was significantly lower as compared to Watson V (32.4 liters $\pm$ 7.2 vs. 34.9 liters $\pm$ 6.1). The effect of the use of this new methodology on Kt/V agreements between ionic dialysance and urea kinetic modeling is a focus for further studies.

Concluding, ionic dialysance has greatly facilitated the assessment of Kt/V , and appears to be relatively widely used in European centers according to a recent

survey³³. However, still discrepancies between ionic dialysance and formal urea kinetic modeling are observed, which depend among others on the method used to assess ionic dialysance, on the methods of blood sampling, and on the methods used for determination of the urea distribution volume. In general, underestimation of spKt/V by Diascan® would have less serious consequences as compared to overestimation.

Due to the still existing controversies with regard to ionic dialysance, it appears prudent to assess Kt/V by formal urea kinetic modeling once monthly in accordance with current guidelines. And moreover to use ionic dialysance as a tool to detect disturbances in delivery of dialysis dose, e.g. by access circulation or frequent treatment interruption, which would remain undetected if only assessed by once-monthly adequacy monitoring.

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Samenvatting en conclusies

Samenvatting

Dit proefschrift bestaat uit twee delen: het eerste deel richt zich op verschillende aspecten met betrekking tot natriumbalans tijdens de hemodialyse behandeling. Deze werd onderzocht tijdens reguliere hemodialysebehandelingen, maar ook tijdens alternatieve hemodialysebehandelingen, zoals hemodialyse met behulp van bio-feedback of natriumprofielen.

Het tweede deel richt zich op het monitoren van de effectiviteit van de dialyse behandeling. Dit werd onderzocht door middel van conventionele ureumkinetiek en door middel van ionische dialysance.

Deel 1

Validatie van plasma/dialysaat geleidbaarheid en ionische massa balans metingen

In dit proefschrift, worden de benamingen plasma natrium/plasma geleidbaarheid, dialysaat natrium/dialysaat geleidbaarheid en natriumbalans/ionische massa balans naast elkaar gebruikt met een overeenkomende betekenis.

Het belangrijkste voordeel van plasma geleidbaarheid en ionische massabalans is dat ze allebei non-invasief gemeten kunnen worden (zonder bloedafname) en zijn, met behulp van deze technologie (Diascan®; Hospal-Gambro) elke dialysebehandeling beschikbaar*:

*in dit proefschrift is voor het gemak (maar wel in overeenstemming met de literatuur) de term plasma geleidbaarheid gebruikt, terwijl Diascan® eigenlijk de geleidbaarheid in plasma water berekent

Zoals in de Introductie uitgebreid beschreven is, is de geleidbaarheid van een oplossing gelijk aan het vermogen om elektrische stroom te geleiden. Plasma geleidbaarheid wordt beoordeeld aan de hand van een eenvoudige wiskundige formule, welke rekening houdt met ionische klaring en veranderingen in de geleidbaarheid van de dialysaatuitgang na een tijdelijke verhoging van de geleidbaarheid aan de dialysaatingang tijdens de dialysebehandeling:

Eerdere onderzoeken hebben al een bijna lineaire relatie aangetoond tussen plasma natrium en plasma geleidbaarheid op basis van onderstaande formule:

Plasma natrium = (Plasma geleidbaarheid x 10.4) – 9.57¹. Gebaseerd op resultaten van verschillende studies mag aangenomen worden dat plasma geleidbaarheid voldoende is gevalideerd om deze als surrogaat voor plasma natrium te mogen gebruiken. Echter dient wel in aanmerking genomen te worden dat andere ionen ook, in geringere mate, de plasma geleidbaarheid kunnen beïnvloeden.

Ditzelfde geldt voor de relatie tussen dialysaat geleidbaarheid en dialysaat natrium, omdat de totale geleidbaarheid ook beïnvloed wordt door andere ionen zoals chloride en bicarbonaat, die kunnen veranderen door de dialysebehandeling. In **hoofdstuk 3 en 4** wordt wel ingegaan op de verschillende methoden van natriumbepalingen, maar worden deze niet gedetailleerd beschreven. Bij een ingestelde dialysaat geleidbaarheid van 14.0 mS/cm, waren dialysaat natrium bepalingen door middel van vlamfotometrie en indirecte ionometrie vergelijkbaar (140.4±1.5 en 139.9±0.7 mmol/l), maar weken af indien ze bepaald werden met behulp van directe ionometrie (135.4±1.1 mmol/l). Zoals in de Introductie al beschreven, komt dit waarschijnlijk door complexvorming van natrium met andere ionen in het dialysaat, wat niet gemeten wordt door directe ionometrie. Daarom, zoals la Milla ook al concludeerde³, is de bepaling van natrium uit verzameld dialysaat afhankelijk van de gebruikte methode en verdienen bepalingen door middel van indirecte ionometrie en vlamfotometrie de voorkeur.

Voor de ionische massa balans (IMB) als surrogaat voor natriumbalans tijdens de dialysebehandeling zijn er minder gegevens beschikbaar in de literatuur. Lambie zag een significante relatie tussen deze twee methoden door gebruik te maken van een formule die gebaseerd is op veranderingen in plasma natrium tijdens de dialysebehandeling en ultrafiltratievolume². In **hoofdstuk 4** werd de ionische massa balans gevalideerd ten opzichte van de natriumbalans door dialysaat te verzamelen tijdens de dialysebehandeling, waaruit natrium werd bepaald door middel van vlamfotometrie, en te vergelijken met de getelde ionen door de dialysemachine (Diascan®). Ook in dit onderzoek werd een sterke relatie gevonden tussen natrium balans en ionische massa balans [$r^2=0.95$], hoewel er binnen de individuele patiënt-metingen wel discrepanties gezien werden tussen de beide methoden. Of deze verschillen met name verklaard worden door de inherente variatie van de natriumbepalingen, of mede door veranderingen in andere ionen in het dialysaat kan niet worden afgeleid worden uit dit onderzoek. In **hoofdstuk 5**, bleken ionische massa balans-metingen door Diascan® significant te correleren met handmatige geleidbaarheids-metingen van het dialysaat.

Samenvattend, met de bovenstaande beperkingen in het achterhoofd houdend, zijn in dit proefschrift

ionische massa balans als surrogaat voor natrium balans,
 plasma geleidbaarheid als surrogaat voor plasma natrium en
 dialysaat geleidbaarheid als surrogaat voor dialysaat natrium gebruikt.

Relatie tussen plasma geleidbaarheid en ionische massa balans

Verwijdering van natrium tijdens dialyse wordt vooral veroorzaakt door convectie. Daarentegen zou ook diffusie, veroorzaakt door verschil in plasma en dialysaat natriumconcentratie, een belangrijke rol kunnen spelen. Dit werd beschreven in **hoofdstuk 3 en 4**, waarin een zeer sterke relatie tussen predialyse plasma geleidbaarheid en diffusieve ionische massa balans werd gezien. Dit werd aangetoond door middel van gerandomiseerd onderzoek tijdens isovolemische dialyse en door middel van retrospectief onderzoek, waar vanuit de database van een dialysecentrum gegevens van alle patiënten gedurende een half jaar werden geanalyseerd.

In het onderzoek met de isovolemische dialyse van **hoofdstuk 3**, waarin 13 patiënten geïncludeerd werden, werd ionisch massa transport van dialysaat naar patiënt gezien vanaf het moment dat de plasma geleidbaarheid 0.2-0.3 mS/cm lager was dan de dialysaat geleidbaarheid, of vanaf het moment dat het plasma natrium 4-5 mmol/lager was dan het dialysaat natrium. In de databasestudie in **hoofdstuk 4**, werd opgemerkt dat diffusief ionisch massa transport van dialysaat naar patiënt optrad als de plasma geleidbaarheid lager was dan 14.25 mS/cm (of plasma natrium lager dan 139 mmol/l) bij een ingestelde dialysaat geleidbaarheid van 14 mS/cm (dialysaat natrium 140 mmol/l). De mogelijke verklaring van de discrepantie tussen deze studies zou kunnen

zijn dat door ultrafiltratie, eiwit coating van de kunstnier optreedt, waardoor het Donnan effect beïnvloed wordt en daardoor de diffusieve ionische massa balans. Daarnaast zouden pH veranderingen tijdens de dialysebehandeling het Donnan effect ook kunnen beïnvloeden^{4,5}.

In het onderzoek, beschreven in **hoofdstuk 4**, bleek dat diffusieve ionische massa balans voor gemiddeld $18.3 \pm 16.7\%$ deel uit maakte van de totale ionische massa balans. Maar, uit de grote range [0.4 - 75.3%] bleek dat binnen de individuele patiënten, diffusieve ionische massa balans soms een groot onderdeel is van de totale ionische massa balans.

Verschillende andere studies hebben ook het effect van dialysaat natrium op natriumbalans tijdens dialyse bestudeerd. In het onderzoek van Song, trad diffusieve natriuminflux op bij een dialysaat natrium vanaf 137.8 mmol/l⁶, terwijl Flanigan bij een groot aantal patiënten interdialytische plasma natrium stijging zag tijdens een dialysaat natrium instelling van 140 mmol/l⁷. Of het kleine verschil tussen deze studies toegeschreven kan worden aan verschillen in kunstniereigenschappen (b.v. door eiwit adsorptie) of ultrafiltratiesnelheid is niet verder uitgezocht.

Conclusie: er is een sterke relatie tussen pre-dialytisch plasma natrium, dialysaat natrium en ionische massa balans. Volgens de beschreven resultaten van **hoofdstuk 4**, wordt er geen belangrijke diffusieve natriuminflux van dialysaat naar patiënt verwacht wanneer de dialysaat natriumconcentratie lager of gelijk is aan de pre-dialytische plasma natriumconcentratie.

Een belangrijke extrapolatie van **hoofdstuk 3 en 4**, en van studies van anderen, is dat er bij gebruik van dialysaat natrium van 140 mmol/l, diffusief natriumtransport van dialysaat naar patiënt kan optreden bij patiënten met een laag pre-dialytisch plasma natrium. Dit is van belang, omdat het pre-dialytische plasma natrium bij een aanzienlijk deel van de patiënten lager ligt dan 140 mmol/l. Bij 33% van de patiënten uit **hoofdstuk 4**, werd diffusieve natriuminflux en verhoging van de plasma conductiviteit gezien, alhoewel bij bijna alle patiënten totaal ionisch massaverlies van patiënt naar dialysaat werd gezien door convectieve verwijdering. Volgens de literatuur wordt in het algemeen aangenomen, dat bij gebruik van dialysaat natriumconcentratie van ongeveer 137-138 mmol/l een redelijke balans wordt bereikt tussen, aan de ene kant het voorkomen van natriuminflux tijdens de dialyse en aan de andere kant effecten van een te lage natriumconcentratie op bloedvolume-preservatie^{8,9}. Bijvoorbeeld, leverde het verlagen van dialysaat natrium van 141 naar 138 mmol/l op een dialyse afdeling een kleine verbetering in bloeddruk op, terwijl de hypotensieve periodes tijdens de dialysebehandeling niet toenamen⁸. Tijdens een audit van 2187 patiënten, werd gebruik van dialysaat natriumconcentratie van 140 mmol/l of hoger geassocieerd met meer interdialytische gewichtstoename, hogere polsdruk, en zelfs met een hogere incidentie van intradialytische hypotensieve

episodes vergeleken met patiënten waarbij een dialysaat natrium van 136 of 137 mmol/l⁹ werd gebruikt.

Of vooral patiënten met een laag pre-dialytisch plasma natrium en patiënten met moeilijk te behandelen hypertensie zouden kunnen profiteren van het verder verlagen van het dialysaat natrium (b.v. tot 136 mmol/l) is een interessant onderwerp voor toekomstig onderzoek. In een recente studie van Lambie et al., werd bij sommige patiënten een verlaging van dialysaat geleidbaarheid tot 13.0 mS/cm bereikt, met bijkomende voordelen zoals bloeddrukverlaging en verlaging van interdialytische gewichtstoename. Patiënten, die regelmatig intradialytische hypotensieve periodes hadden, werden echter niet geïnccludeerd in het onderzoek².

Effecten van alternatieve hemodialysebehandelingen op natriumbalans en plasma geleidbaarheid

Alhoewel een dialysaat natrium van 137-138 mmol/l bij de meerderheid van de patiënten adequaat lijkt, worden hogere dialysaat natriumconcentraties en/of natriumprofielen regelmatig op dialyseafdelingen gebruikt om intradialytische hypotensie te voorkomen. De verbetering van refill van bloedvolume vanuit het interstitium tijdens ultrafiltratie, opgewekt door de natriumgradiënt, ligt aan dit gebruik ten grondslag. Echter, zijn de effecten hiervan op de natriumbalans niet onderzocht.

Gebaseerd op de resultaten van **hoofdstuk 3**, is ionische massabalans een acceptabel instrument om de verschillen in natriumbalans tussen de verscheidene behandelingen te vergelijken. Ionisch massa transport van patiënt naar dialysaat (als surrogaat voor natriumverlies) was significant lager bij dialysebehandelingen die uitgevoerd werden met een (hypertone) dialysaat natriumconcentratie van 144 mmol/l [80 mmol] vergeleken met een dialysaat natriumconcentratie van 140 mmol/l. In het onderzoek beschreven in **hoofdstuk 5**, waarbij verschillende technieken werden uitgevoerd (gedurende 11 opeenvolgende behandelingen) om intradialytische hypotensie te voorkomen, (inclusief natriumprofiel) werd een verschil in ionische massa balans alleen gezien tijdens de eerste behandeling met een natriumprofiel, terwijl bij de volgende behandeling de predialytische plasma conductiviteit duidelijk verhoogd was tijdens de beginsituatie. Waarschijnlijk is de afwezigheid van verschil in ionische massabalans na de eerste behandeling het gevolg van de sterke relatie tussen de ionische massabalans en de predialytische plasma conductiviteit. Tijdens de behandelingen met natriumprofiel, waarbij de pre-dialytische plasma geleidbaarheid steeg, bleef de ratio tussen de predialytische plasma geleidbaarheid en dialysaat geleidbaarheid hetzelfde, waardoor de ionische massabalans hetzelfde bleef. Deze resultaten komen overeen met die van Lambie et al, waarbij een geleidelijke verlaging van de dialysaat geleidbaarheid alleen tijdens de eerste behandeling met de nieuwe dialysaatinstelling resulteerde in een verandering van de ionische massa balans².

Stijging van de plasma geleidbaarheid door de dialysebehandeling is in strijd met het model van een stabiel individueel plasmanatrium^{4,7,11,12}. Dit model gaat ervan uit dat natriuminflux tijdens de dialysebehandeling tot gevolg heeft dat de patiënt meer dorst krijgt en meer gaat drinken, waardoor de plasma natriumconcentratie niet verandert. In overeenkomst met resultaten van Thein⁸, maar in tegenstelling tot resultaten van anderen^{2,6,12}, veroorzaakten veranderingen in dialysaat natriuminstellingen veranderingen in plasma geleidbaarheid, maar niet in meer vochtintake. Of in onze studie de patiënten wel meer dorst hadden, door stijging van de plasma geleidbaarheid, maar niet meer interdialytische gewichtstoename lieten zien (door b.v. een stabiele vochtcompliance), is niet onderzocht.

Literatuur toont aan, dat natrium profielen de oorzaak kunnen zijn van verhoogde interdialytische gewichtstoename, hypertensie en effecten op de plasma geleidbaarheid zoals die in **hoofdstuk 5** beschreven zijn, waardoor gebruik van hypertone natriumprofielen wordt afgeraden om intra-dialytische symptomen te voorkomen. Interessant genoeg, ook al was het aantal geïncludeerde patiënten laag, bleek in **hoofdstuk 5** bloedvolume-gecontroleerde feedback een effectieve techniek om intra-dialytische hypotensie te voorkomen, zonder nadelige effecten op de zoutbalans. Bloedvolume-gecontroleerde feedback is een technologie waarbij op basis van metingen van bloedvolume-refill continu met ultrafiltratiesnelheid wordt gevarieerd, om zo een te snelle bloedvolumedaling (met als gevolg evt. hypotensie) te voorkomen. De effectiviteit van deze biofeedback technologie komt overeen met andere studies, ook van onze dialyse afdeling^{13,14}.

Ook werd er geen verschil van zoutbalans gevonden tijdens het gebruik van plasma geleidbaarheid-gecontroleerde feedback vergeleken met standaard hemodialyse. Plasma geleidbaarheid-gecontroleerde feedback is een technologie, waarbij op basis van online gemeten plasma conductiviteit de dialysaat conductiviteit zodanig varieert, zodat een vooraf ingestelde einddialyse plasma conductiviteit wordt behaald. In deze studie werd, in overeenstemming met de beschikbare literatuur op dat moment, gekozen voor een doel plasma natriumconcentratie van 14.0 mS/cm (of plasma natrium van ± 138 mmol/l). Echter bij deze instelling, zou bij een aantal patiënten met een laag predialytisch plasma natrium, diffusieve natrium influx opgetreden kunnen hebben. Daarom, zou vooral voor deze patiëntengroep individualisatie van dialysaat natrium een goede optie kunnen zijn.

Individualisatie van dialysaat natrium

Er zijn weinig gegevens over individualisatie van dialysaat natrium beschikbaar in de literatuur. In het onderzoek, beschreven in **hoofdstuk 3**, resulteerde individualisatie van dialysaat natrium in een verhoging van natriumverwijdering tijdens dialyse bij patiënten met een laag pre-dialytisch plasma natrium, maar in een vermindering van natriumverwijdering bij patiënten met een hoger pre-dialytisch plasma natrium ten

opzichte van een dialysebehandeling met de standaardinstelling. Om die reden, in ieder geval vanuit theoretisch oogpunt, wordt verwacht dat vooral patiënten met een laag pre-dialytisch plasma natrium zouden kunnen profiteren van een geïndividualiseerd dialysaat natrium. In het onderzoek van de Paula¹⁸, werd dialysaat natrium geïndividualiseerd, door handmatig het dialysaat natrium aan te passen aan het pre-dialytisch plasmawater natrium met een correctiefactor voor het Donnan effect. Dit resulteerde in vermindering van de hypertensie en vermindering van de inter-dialytische gewichtstoename. Tegelijkertijd verminderde de incidentie van intra-dialytische hypotensie vergeleken met dialysebehandelingen met een vast dialysaat natrium van 138 mmol/l. In dit onderzoek behaalden vooral patiënten met moeilijk te behandelen hypertensie voordeel van het verlagen van het dialysaat natrium. Pre-dialytisch plasma natrium was voor de start van het onderzoek al vrij laag (134.0 ± 1.4 mmol/l), wat veroorzaakt werd doordat patiënten met hogere plasma natriums geëxcludeerd werden. Vergelijkbaar onderzoek werd gedaan door Sayarlioglu¹⁹, waarbij de predialytische bloeddruk en interdialytische gewichtstoename afnamen op het moment dat het dialysaat natrium geïndividualiseerd werd bij patiënten met pre-dialytische plasma natrium waarden die lager waren dan de standaard gebruikte dialysaat natriumconcentratie. In deze studies werden alleen stabiele patiënten geïnccludeerd, zonder frequente hypotensieve episodes.

Al met al, hoewel er meer onderzoek nodig is, lijkt het individualiseren van dialysaat natriumconcentratie een veelbelovend instrument, vooral bij patiënten met lage pre-dialytische plasma natriumwaarden, hoge interdialytische gewichtstoenames en ongecontroleerde hypertensie. Daarentegen, zou meer informatie over variaties in pre-dialytisch plasma natrium (of geleidbaarheid) zinvol zijn, omdat tegenstrijdige informatie uit de literatuur de zin van een vast individueel dialysaat natrium bestrijdt.

Variaties in pre-dialytische plasma geleidbaarheid

Om de individuele variaties in pre-dialytische plasma geleidbaarheid te onderzoeken, is er een retrospectieve analyse uitgevoerd, beschreven in **hoofdstuk 4**, van alle dialysebehandelingen op een dialyse afdeling gedurende 6 maanden, waarbij plasma geleidbaarheid werd gebruikt als surrogaat voor plasma natrium. In dit onderzoek, was de gemiddelde variatie-coëfficiënt van pre-dialytische plasma geleidbaarheid 1.3%. Opvallend was het gemiddelde intra-individuele verschil van ± 0.9 mS/cm [$\sim$ plasma natrium 9 mmol/l] tussen de hoogste en de laagste plasma geleidbaarheid tijdens de follow up van zes maanden. Opmerkelijk is, dat inter- en intradialytische verschillen in pre-dialytische plasma geleidbaarheid correleerden met variaties in pre-dialytische bloeddruk, wat een bijkomstig bewijs zou kunnen zijn voor volumeonafhankelijke effecten van natrium op bloeddruk. Natuurlijk is hierin veel meer onderzoek nodig.

Ondanks het feit dat de intrapatiënt variaties vrij gering waren, trekken de resultaten van **hoofdstuk 4 en 5** het bestaan van een gefixeerde dialysaat natriumconcentratie

per patiënt in twijfel. Indien individualisering van de behandeling strategie wordt, zal plasma natrium of plasma geleidbaarheid regelmatig bepaald moeten worden. De online beschikbaarheid op de dialysemachine van plasma geleidbaarheid lijkt een zeer handig instrument om individualisatie van dialysaat natrium te bereiken, zonder dat daar bloedafnames voor nodig zijn. Meer onderzoek zou zich hierop moeten concentreren.

Deel 2

Beoordeling van dialyse adequaatheid door middel van ureum kinetiek: is er een voorkeur methode?

Kt/V_{ureum} is de meest gebruikte parameter ter beoordeling van de adequaatheid van de dialysebehandeling. De uitkomst van deze parameter is een getal, wat aangeeft hoe vaak de V (berekend ureumdistributievolume per individuele patiënt) geklaard is van ureum (en andere kleinmoleculair stoffen) tijdens de totale tijd van de dialysebehandeling. Binnen de meest invloedrijke richtlijnen over dit onderwerp, bijvoorbeeld de European Best Practice Guidelines (EBPG) and Kidney Disease Outcomes Quality Initiative (K-DOQI) is er echter enige discrepantie met betrekking tot de methodiek van de Kt/V bepalingen. Aan de ene kant, adviseert K-DOQI het gebruik van single-pool Kt/V (spKt/V) metingen, terwijl EBPG het gebruik van double-pool of equilibrated Kt/V (eKt/V) onderschrijft, omdat deze voor ureum rebound corrigeert^{20,21}. Uiteindelijk is eKt/V alleen een wiskundige correctie op de formule van spKt/V waarvoor geen extra bloedmonster nodig is. Beide richtlijnen adviseren het gebruik van de ureum reductie rate (URR) alleen als aanvulling bij het beoordelen van dialyse adequaatheid.

Het is niet bekend tot welke hoogte er discrepantie zou kunne bestaan tussen de verschillende formules in de beoordeling van de adequaatheid van de dialysebehandeling. In **hoofdstuk 7** is deze vraag onderzocht bij 830 patiënten van de NECOSAD database. eKt/V boven 1.2, spKt/V boven 1.4 en URR boven 70% werden gebruikt als adequaatheids doelen, en respectievelijk 1.0, 1.2 en 65% als adequaatheids minimum.

Alleen 5% van de patiënten met een spKt/V boven 1.4 had een eKt/V onder 1.2. Bij deze “gemisclassificeerde” patiënten was de gemiddelde eKt/V 1.19, dus erg dicht bij het adequaatheids doel. Het percentage “gemisclassificeerde” patiënten was hoger als URR was gebruikt als formule voor adequaatheid. Min of meer dezelfde percentages “gemisclassificeerde” patiënten werden gevonden als de minimum adequaatheid werd vergeleken. Bij mortaliteitsanalyse werden eKt/V, spKt/V en URR die onder het minimum adequaatheidsniveau werden beoordeeld geassocieerd met

een hoger risico op overlijden, wat het klinisch nut van deze formules bij dialysebehandelingen aantoont.

Vanuit de resultaten van **hoofdstuk 7** kan geconcludeerd worden, dat gebruik van eKt/V of $spKt/V$ niet zoveel uitmaakt voor het beoordelen van de dialyse adequaatheid, onder voorwaarde dat er goede afkappunten worden aangehouden. Het risico van “misclassificatie” wordt wat groter bij gebruik van URR, maar of dit ook invloed heeft op andere patiëntuitkomsten kan niet uit dit onderzoek herleid worden.

Beoordeling van dialyse adequaatheid door middel van ionische dialysance

Voor Kt/V bepalingen zijn bloedafnames nodig. Zoals in de introductie van dit proefschrift beschreven is, is Kt/V bepaling door middel van ionische dialysance een non-invasieve methode die het mogelijk maakt om tijdens elke dialysebehandeling dialysaat adequaatheid te beoordelen zonder bloed af te nemen. Dit kan erg belangrijk zijn gezien de variatie in bereikte Kt/V tussen verschillende behandelingen bij dezelfde patiënt, welke niet opgemerkt wordt wanneer de Kt/V alleen maandelijks bepaald wordt met behulp van bloedafnames. Deze variaties in Kt/V werd gerapporteerd in **hoofdstuk 8**, als bevestiging van eerder onderzoek²². Ook al zijn dialysance (diffusief transport van een oplossing door een semipermeabel membraan) en klaring (verwijdering van een oplossing uit een substantie) een heel ander concept, toch kan ionische dialysance gebruikt worden om ureumklaring tijdens hemodialyse te beoordelen²³.

Kort samengevat, kan ionische dialysance gebruikt worden als surrogaat voor ureumklaring, omdat deze én dezelfde eigenschappen van transport door een kunstnier hebben én dezelfde osmotische distributievolumes in het bloed. Zoals te zien op de figuur op pagina 152, wordt ionische dialysance (door Diascan®) gemeten door veranderingen bij de dialysaattuitgang te beoordelen aan de hand van veranderingen in de dialysaatingang tijdens de dialysebehandeling. De veranderingen van deze dialysaattuitgang worden meegenomen om de ionische dialysance te berekenen, ervan uitgaand dat de plasma geleidbaarheid tijdens die meting niet verandert²⁴. Een zeer sterke relatie tussen ionische dialysance en ureumklaring werd gesignaleerd. Echter lijkt ionische dialysance de ureumklaring iets te onderschatten, hetgeen ook de relatie tussen Kt/V met behulp van ureumkinetiek en met behulp van ionische dialysance zou kunnen beïnvloeden^{24,25}.

Figuur 9.1 Schema van de ingang- en uitgangdialysaat geleidbaarheid tijdens een meting van de ionische dialysance (D), waarbij X_1 en X_2 twee waarden zijn van ingang dialysaatgeleidbaarheid, Y_1 en Y_2 de twee gemeten waarden van de uitgang dialysaatgeleidbaarheid en C_p de geschatte plasma geleidbaarheid van de patiënt. Q_D is dialysaatflow, Q_f ultrafiltratiesnelheid

Overeenkomst tussen ionische dialysance en ureumkinetiek bij het beoordelen van Kt/V

Ook al is Kt/V met behulp van ionische dialysance een single pool methode, toch valt deze berekening lager uit dan wanneer die berekend is volgens sp Kt/V met ureumkinetiek, blijkt uit de resultaten beschreven in **hoofdstuk 8** en in andere studies uit de literatuur²⁴.

Naast de (geringe) onderschatting van de ureumklaring door ionische dialysance komt dit onder andere ook door de methode waarmee het ureum distributie volume (V) berekend wordt, zoals in de volgende paragraaf uitgebreider wordt besproken. Deze dient in de formule Kt/V bij gebruik van ionische dialysance (K) ingevoerd te worden, waardoor de V een aanmerkelijke invloed krijgt op de daadwerkelijke uitkomst.

De Watson formule wordt, als bekendste antropometrische formule, meestal gebruikt om deze V te berekenen, maar deze formule heeft de neiging om het ureum distributie volume bij dialysepatiënten te overschatten, waardoor de uiteindelijke Kt/V te laag uitvalt. Echter, zelfs wanneer V wordt berekend met een exactere formule volgens het ureumkinetiek model, laat Kt/V gemeten door Diascan® (een single pool methode), meer overeenkomst zien met e Kt/V dan met sp Kt/V (**hoofdstuk 8**). Deze goede correlatie tussen e Kt/V en Kt/V met behulp van ionische dialysance komt overeen met de resultaten van McIntyre et al.²⁶.

Een andere factor die de oorzaak zou kunnen zijn, van het lager uitvallen van de Kt/V door middel van ionische dialysance vergeleken met de Kt/V door middel van ureumkinetiek, is het cardiopulmonale recirculatie effect. Cardiopulmonale recirculatie bestaat uit het effect dat een gedeelte van het gezuiverde bloed dat via de arterioveneuze shunt terug gaat naar het lichaam, direct via het hart weer de arteriële aansluiting van de arterioveneuze shunt bereikt, zonder eerst weer via lichaamsweefsels afvalstoffen op te nemen. Dit fenomeen is per definitie altijd aanwezig tijdens hemodialyse, waarbij gebruik wordt gemaakt van een arterioveneuze shunt en nooit aanwezig tijdens hemodialyses via een centraal veneuze catheter.

Een andere reden, die de onderschatting van Kt/V door middel van ionische dialysance zou kunnen verklaren, zou het effect van de geleidbaarheids-pulsen op de plasma geleidbaarheid kunnen zijn. Bij de berekening van de ionische dialysance, wordt ervan uitgegaan dat de plasma geleidbaarheid constant blijft, ondanks de geleidbaarheids-pulsen tijdens die meting. Het constant blijven van de plasma geleidbaarheid tijdens de ionische dialysance meting is in twijfel getrokken door Gotch, die beweerde dat de geleidbaarheids-pulsen voor extra natriumbelasting zorgden en vervolgens voor verhoging van de plasma geleidbaarheid²⁸. In **hoofdstuk 6**, is het effect van deze geleidbaarheids-pulsen op de ionische massabalans onderzocht. Geen verschil werd gezien tussen behandelingen met of zonder Diascan® metingen in ionische massa balans. Op zich is dit geen definitief argument voor het niet optreden van tijdelijke natriumbelasting door geleidbaarheids-pulsen, maar het lijkt vooralsnog, dat vooral de bevinding van Marcadel over aan- of afwezig zijn van de pulmonale recirculatie (die hierboven beschreven is) van groter belang lijkt voor het verschil tussen ureumklaring en ionische dialysance²⁷.

In Nederland zijn verschillende merken dialyse machines beschikbaar met allen vergelijkbare technische opties om Kt/V ²⁹ te meten. Interessant is wel, dat bijvoorbeeld de OCM®-monitor (online clearance monitor) van Fresenius en de Diascan® van Gambro een andere manier toepassen om de geleidbaarheids-pulsen te doseren. Diascan® verhoogt de geleidbaarheid gedurende korte tijd tijdens de puls met 1mS/cm, terwijl OCM® gebruikt maakt van een drie fase geleidbaarheids-puls met een langere stabilisatietijd²⁴. Of deze methodologische verschillen resulteren in verschillen tussen de beide methodes dient verder onderzocht te worden.

Ureum distributie volume

Verschillen tussen ionische dialysance en de standaard ureumkinetiek voor het bepalen van de dialyse-effectiviteit, zijn ook afhankelijk van de methode die gebruikt wordt om het ureum distributie volume (V) te bepalen. Hiervoor is het effect van de cardio pulmonale recirculatie op de berekening van de ionische dialysance al besproken. Daarnaast is het effect van de meest gebruikte *antropometrische formules*

(b.v. Watson) om V te berekenen een andere reden voor het verschil, omdat deze formules het ureum distributie volume overschatten.

Deze overschatting kan verklaard worden, omdat antropometrische formules uitgaan van een standaard lichaamsverdeling, terwijl bij dialysepatiënten vaker het spierweefsel afneemt en het vetweefsel relatief toeneemt³⁰. Anderzijds zal de redistributie van het ureum naar centrale lichaamscompartimenten (door verminderde perfusiedruk in de perifere compartimenten), als gevolg van de dialysebehandeling, bijdragen aan een overschatting van het ureum distributie volume bij gebruik van de ureumkinetische methode.

In **hoofdstuk 8** werd aangetoond, dat indien gebruik gemaakt wordt van de *kinetische formule* om het ureum distributie volume te berekenen, de relatie tussen ionische dialysance en ureumkinetiek (door middel van bloedafnames) sterker werd. Dit komt overeen met de resultaten van di Filippo³¹. Helaas is deze vorm van berekenen ingewikkeld voor de dagelijkse praktijk en zijn er ook weer bloedafnames nodig om deze te kunnen berekenen. Indien gebruik gemaakt werd van de *ionische dialysance formule* om het ureum distributie volume te bepalen was er tevens een goede correlatie, maar deze formule bleek niet betrouwbaar bij patiënten met restnierfunctie. Beide formules blijken niet betrouwbaar indien recirculatie van de shunt aanwezig is.

Daarom, blijft de vraag, of er andere methodes mogelijk zijn om het ureum distributie volume te berekenen, die makkelijk uitvoerbaar zijn in de dagelijkse praktijk. Bioïmpedantie meting, waarbij het totale lichaamswater wordt geschat, door elektrische geleiding van een wisselstroom door het lichaam, is makkelijk uitvoerbaar en non-invasief. Uit recent onderzoek van Lindley et al. bleek (vergelijkbaar met de resultaten uit **hoofdstuk 8**) een onderschatting van de dialyse-effectiviteit indien *antropometrische formules* (b.v. Watson) werden gebruikt, terwijl het gebruik van bioïmpedantie resulteerde in vergelijkbare Kt/V uitkomsten als met behulp van de *kinetiek formule* om het ureum distributie volume te berekenen³². Uit een vooronderzoek van onze dialyse afdeling bleek ook, dat het ureum distributie volume, indien het gemeten werd door de bioïmpedantie methode BCM® (Fresenius), significant lager was dan wanneer deze gemeten werd door de Watson formule (32.4 liters $\pm$ 7.2 versus 34.9 liters $\pm$ 6.1). Het effect van het gebruik van deze nieuwe methode bij de vergelijking van Kt/V tussen ureumkinetiek en ionische dialysance is een belangrijk onderwerp voor vervolgonderzoek.

Geconcludeerd kan worden, dat ionische dialysance de bepaling van Kt/V een stuk makkelijker maakt, en lijkt ook steeds meer gebruikt te worden in Europese dialysecentra³³. Toch zijn er nog steeds discrepanties tussen ionische dialysance en ureumkinetiek, veroorzaakt door onder andere de methode van bepaling van ionische dialysance, de methode van laboratoriumbepaling en de methode om het ureum distributie volume te bepalen. In het algemeen kan wel gesteld worden, dat een

onderschatting van de spKt/V door Diascan® minder schadelijke gevolgen zal hebben dan indien dit een overschatting zou zijn.

Met in acht neming van bovenstaande bezwaren, zou ionische dialysance een goed middel kunnen zijn om de dialyse effectiviteit te bewaken. Als tijdens elke dialysebehandeling de ionische dialysance wordt gecontroleerd kan, door deze trend te bewaken, geanticipeerd worden op elke verandering in dialyse adequaatheid, b.v. door shuntrecirculatie, regelmatige onderbrekingen van de behandeling, verkeerd aansluiten van dialyselijnen of dialysaatkoppelingen en het niet behalen van de voorgeschreven bloedflow. Dit zou normaal pas opgemerkt worden op het moment dat de dialyse adequaatheid door middel van ureumkinetiek (bloedafnames) gemeten wordt (1 keer per maand), of helemaal niet.

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Dankwoord

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Curriculum Vitae

Curriculum Vitae

Karin Moret werd op 21 april 1968 geboren in Eindhoven. Zij voltooide in 1988 het atheneum aan het Bisschoppelijk College te Weert. In datzelfde jaar begon zij de inservice opleiding voor A-verpleegkundige van het (destijds nog) st Joseph Ziekenhuis in Eindhoven en rondde deze in 1992 af. Na een jaar als invalkracht op verschillende verpleegafdelingen van het Máxima Medisch Centrum in Veldhoven gewerkt te hebben, begon zij in 1993 op de dialyse afdeling, waar zij in 1994 de opleiding voor dialyseverpleegkundige afrondde. Vanaf 1999 hield zij zich daar onder andere bezig met onderzoek, waarvoor zij in 2000 de post-HBO opleiding researchcoördinator bij de Transfergroep in Rotterdam volgde. Daarnaast was zij tot 2004 werkzaam als kwaliteitsmedewerker en was zij bestuurslid van de L.V.D.T. Na een aantal jaren actief te zijn geweest als onderzoeksverpleegkundige voor diverse externe studies, startte zij in 2001 met eigen onderzoek in samenwerking met het Maastrichts Universitair Medisch Centrum. Gestart werd met onderzoek naar de meerwaarde van bloedvolume gestuurde ultrafiltratie met de dialysemachine (Hemocontrol). Daarna werd dit uitgebreid naar andere opties van deze machine. Een deel van dit onderzoek is beschreven in dit proefschrift.