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Use of Online Conductivity Monitoring to Study Sodium Mass Balance in Chronic Haemodialysis Patients: Prospects for Treatment Individualisation

Aghogho Odudu[a] Stewart Lambie[a] Maarten W. Taal[a] Richard J. Fluck[a]
Christopher W. McIntyre[a, b]

[a]Department of Renal Medicine, Royal Derby Hospital, Derby, and [b]School of Graduate Entry Medicine and Health, University of Nottingham, Nottingham, UK

Key Words
Online conductivity monitoring · Sodium mass balance · Chronic haemodialysis patients

Abstract
Background: Failure to achieve isonatric haemodialysis (HD) drives an expansion of extracellular volume leading to increased interdialytic weight gain (IDWG). This may be a causative factor in the development of HD-induced cardiac injury. We examined total and diffusive sodium mass balance during HD. ***Methods:*** 24 chronic HD patients using a fixed 140 mmol/l sodium concentration were studied over 4 weeks. Dialysate and plasma conductivity and ionic mass balance (IMB) were recorded. IMB estimates total ionic transfer across the HD membrane. ***Results:*** Mean total IMB was 338 mmol indicating net sodium removal. Intrapatient variability was less than interpatient variability (coefficient of variation = 42 vs. 26%, respectively). The diffusive component of ionic mass balance (IMB_{diff}) was 97 ± 18 mmol approximating 29% (±22–36) of total sodium removal. IMB_{diff} also correlated with both plasma conductivity and predialysis plasma sodium ($r^2 = 0.82$ and 0.6, respectively; $p < 0.0001$) as well as the reduction in plasma conductivity and plasma sodium during HD ($r^2 = 0.7$ and 0.5, respectively; $p < 0.0001$). ***Conclusion:*** HD against a fixed dialysate sodium concentration of 140 mmol/l results in a wide range of sodium removal with a mean of 29% removed by diffusion. Online conductivity monitoring can be utilized as part of a variety of strategies to enable the delivery of individualised and isonatric HD. Further study is required to explore the utility of such strategies which may be crucial in reducing IDWG and HD-induced cardiac injury.

Introduction

It is well recognised that haemodialysis (HD) patients suffer excess cardiovascular morbidity and mortality [1]. It is also becoming appreciated that this rate of cardiovascular attrition is not driven by the same variety of traditional risk factors or pathophysiological processes that are important in the general population [2]. There is growing evidence focusing on the mechanisms underpinning this excess cardiac mortality including HD-induced cardiac injury [3]. The historical focus on small solute clearance precipitated by the NCDS study, improvements in HD technology and economic factors have driven an inexorable pressure to reduce treatment times

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Dr. C.W. McIntyre
Department of Renal Medicine
Royal Derby Hospital
Uttoxeter Road, Derby DE22 3NE (UK)
Tel. +44 13 32 789 344, E-Mail Chris.McIntyre@nottingham.ac.uk

[4, 5]. This has promoted a reliance on higher dialysate sodium concentrations from 130 to 145 mmol/l or more as this is thought to reduce adverse intradialytic symptoms and haemodynamics associated with shorter treatment times [6]. However, truly adequate dialysis should be isonatric allowing for complete removal of the *inter*dialytic sodium gain and avoiding *intra*dialytic sodium loading and consequently higher interdialytic weight gain (IDWG) [7]. Increased IDWG or increased ultrafiltration volumes are associated with increased blood pressure (BP), left ventricular mass and mortality [8–11]. Furthermore, we have identified ultrafiltration volume as a potent and modifiable determinant of HD-induced myocardial stunning and this may be an integrating factor linking IDWG to excess mortality [12]. The terminology of 'high' and 'low' dialysate sodium concentrations can be unclear. Only the ionized proportion of sodium is available for diffusion, hence its movement is determined by the gradient between the concentrations of non-complexed, electrochemically active ions from plasma to dialysate as well as temperature and acidity. The Gibbs-Donnan effect refers to a phenomenon caused by anionic plasma proteins too large to traverse the dialysis membrane, creating an electric field that attracts cations and reducing the amount of plasma diffusible sodium [13]. This results in a hypotonic ultrafiltrate and allows the movement of sodium and water to become uncoupled during HD [14]. This makes it possible for patients to load sodium during dialysis, despite dialysate sodium concentration being lower than the predialysis plasma sodium concentration (commonly termed 'low' dialysate sodium concentration) [15, 16]. More recently, the non-osmotic storage of sodium in skin and other tissues has been described and this may further allow dissociation of sodium and water handling [17]. Though the effects of this may be negligible over a single HD session, the potential of this reservoir of sodium ions to buffer sodium transport over a longer period and influence BP and IDWG has not been fully elucidated. The picture is complicated further by the methods of measuring sodium. Laboratories typically use flame spectrophotometry or indirect potentiometry with diluted samples to measure total sodium concentration, which is practical for multiple samples. This is typically 4–6% lower than the electrochemical activity of ionised sodium in plasma water measured directly with an ion-selective electrode [18].

This has culminated in a situation where the goal of an individualised isonatric HD prescription has been hampered by the lack of effective and simple tools to study the consequences of dialysate sodium concentration to sodium mass balance in routine clinical practice. Such choices have been largely based on empirical observation. Recent study into the use of online monitoring of plasma conductivity has demonstrated that such technology is capable of accurately estimating sodium mass balance during HD [19–21]. This study aimed to explore the use of online conductivity monitoring and the measurement of ionic mass balance (IMB), to examine sodium removal and the relationships with plasma conductivity, in chronic HD patients. Furthermore, we set out to study the degree of variability in sodium removal (both within individuals and between patients) in an effort to define how this technology might assist in the development of individualised dialysate sodium prescriptions to allow isonatric dialysis.

Methods

Patients

We prospectively studied 24 (21 male, 3 female) stable chronic HD patients for a 4-week period (288 treatments in total). Demographics are summarised in table 1. All had a well-functioning native arteriovenous fistula and were dialysed in a discrete low dependency unit. Patients with diabetes were excluded as there are data suggesting that assessment of sodium mass balance would be significantly confounded by glycaemic control [22]. Upon entry to the study, patients had their dry weight confirmed with reference to clinical examination and serial BP readings. A standard low-sodium diet (<6 g per day) was reinforced, but no additional dietary interventions or assessments were performed. Ten patients were oliguric (defined as urine output of 10–150 ml/day), whilst 14 patients were anuric (defined as urine output less than 10 ml/day). For the purposes of this study, we assumed that these patients had no significant residual renal function. The study was approved by the Derbyshire Research Ethics Committee and all patients gave informed consent (table 1).

HD Schedule

HD was performed using Integra® dialysis monitors equipped with Diascan® conductivity and Hemoscan® haemoglobin concentration monitoring modules (Gambro Hospal, Mirandola, Italy). All patients had 4-hour treatment sessions, 3 times per week using haemophan dialysers (Hospal HG 500–700). Dialysate composition (in mmol/l) was: sodium 140, bicarbonate 32, potassium 1, calcium 1.25, magnesium 0.5, chloride 107.5, glucose 5.6 and acetate 3. Dialysate sodium concentration was measured by flame photospectometry (using an aqueous calibrant) and calibrated against dialysate inlet conductivity. Dialysate inlet conductivity is constrained to no more than 1% drift before automated recalibration (Hospal supplied data) and lack of significant drift was confirmed by review of the recordings of dialysate conductivity for each of the studied treatments. In addition, the dialysis monitor automatically calibrates the conductivity cells against reverse osmosis water at the start of each session. The internal conductivity cells were also calibrated according to the

Table 1. Demographics of study patients (n = 24)

Mean age ± SD, years	62 ± 16
Mean length of time on dialysis ± SD, months	14.8 ± 14.5
Mean baseline serum sodium ± SD, mmol/l	138.8 ± 3.5
Characteristic	
Male:female	21:3
Non-smoker:current smoker	23:1
History of ischaemic heart disease	2
Ethnicity	
Caucasian:Afro-Caribbean	23:1
Causes of end-stage renal disease	
Glomerulonephritis	5
IgA nephropathy	4
Renovascular disease	3
Focal and segmental glomerulosclerosis	2
Polycystic kidney disease	2
Reflux nephropathy	2
Hypertensive nephrosclerosis	1
Obstructive uropathy	1
Cause unknown (small kidneys)	3
Number of BP medications prescribed	
0	7
1	2
2	11
3	4

manufacturer's instructions against reverse osmosis water and a solution of known concentration using a conductivity meter (IBP HDM97BN, Hanover, Germany). Dialysate temperature was 37.0°C, dialysate flow was 500 ml/min, and blood flow was 250–410 ml/min. Anticoagulation was by unfractionated heparin. For each session, net fluid removal was set on an individual basis according to ideal dry weight. No patients underwent sodium or ultrafiltration profiling. Dialysis prescriptions were held on a separate server and downloaded to the patient's dialysis monitor for each treatment. All data were uploaded to patient-specific files at the end of each treatment for subsequent analysis. Manually recorded data included pre- and postdialysis weight, systolic, diastolic and mean arterial BP at 15-min intervals. Intradialytic hypotension was defined as an absolute systolic BP <90 mm Hg or >30% decrease in systolic BP from the predialysis value or any fall in BP requiring intervention.

Assessments of Sodium Mass Balance

Sodium mass balance was estimated by non-invasive, online conductivity monitoring using the Diascan module and ionic dialysance measurements. Based on the theory developed by Polaschegg [23], this system utilises temperature-compensated conductivity probes at both the dialysate inlet and waste dialysate outlet. Dialysate inlet conductivity is transiently increased by about 1 mS/cm for 2 min intermittently throughout the HD session (every 30 min). Measurement of the difference between inlet and outlet conductivity before and after transient increase allows ionic dialysance and effective plasma conductivity to be derived (and continuously displayed on the dialysis monitor) according to formulae detailed in the online supplementary appendix 1 (www.karger.com/doi/10.1159/000329355). The relative contributions of diffusion (IMB_{diff}) and convection to sodium mass balance were estimated according to formulae also detailed in the online supplementary appendix 1. Pre- and postdialysis plasma sodium was sampled once per week during the study period and measured using an indirect ion-selective electrode-based method (interbatch assay coefficient of variation = 0.58–1%).

Statistical Analysis

IDWG is expressed as a percentage of dry weight. All data were analysed using GraphPad Prism version 4.0 for Windows (GraphPad Software, San Diego, Calif., USA). Correlation plots were subsequently analysed by linear regression. Coefficient of determination was calculated from the Pearson correlation or Spearman's rank-order correlation depending on normality. Intrapatient variability was assessed by calculation of the coefficient of variation. Data are expressed as mean ± SEM (95% confidence intervals) unless otherwise stated.

Results

Validation of our estimate for IMB_{diff} derivation for 5 randomly selected patients was shown with an approximately linear fall ($r^2 = 0.89$; fig. S1, see online suppl. appendix 1). With respect to the data in all 24 patients and 288 treatments, there were no episodes of intradialytic hypotension throughout the study period. All patients had net sodium removal during HD with a total IMB of 338 ± 9.4 mmol (range, 320–357). The component of sodium mass balance attributable to diffusion (IMB_{diff}) was 97.1 ± 18.2 mmol (range, 61.3–133.2). The relative contribution of diffusion to total IMB was a mean of 29% (±22–36). Three of the 24 patients experienced negative IMB_{diff}, indicative of a positive dialysate to plasma concentration gradient, resulting in net diffusion of sodium from dialysate into the patient (fig. 1). There was considerable variation in the degree of apparent sodium removal during an HD session between individual patients. Total IMB per session varied widely from 96 to 515 mmol between subjects but the variation within individuals was lower (coefficient of variation = 42 vs. 26%, respectively). Mean ultrafiltration volume was 1.85 ± 0.05 kg (range, 1.74–1.96). IMB_{diff} was highly correlated with both plasma conductivity and plasma sodium concentration at the start of HD ($r^2 = 0.82$ and 0.6, respectively; $p < 0.0001$; fig. 2). IMB_{diff} was also correlated with the reduction in plasma conductivity and plasma sodium during HD ($r^2 = 0.7$ and 0.5, respectively; $p < 0.0001$; fig. 3). Plasma conductivity fell from a mean of 14.16 ± 0.02 mS/cm (range, 14.12–14.20) to 13.76 ± 0.01 mS/cm (range, 13.74–13.78) ($p < 0.0001$). Plasma sodium concentration fell

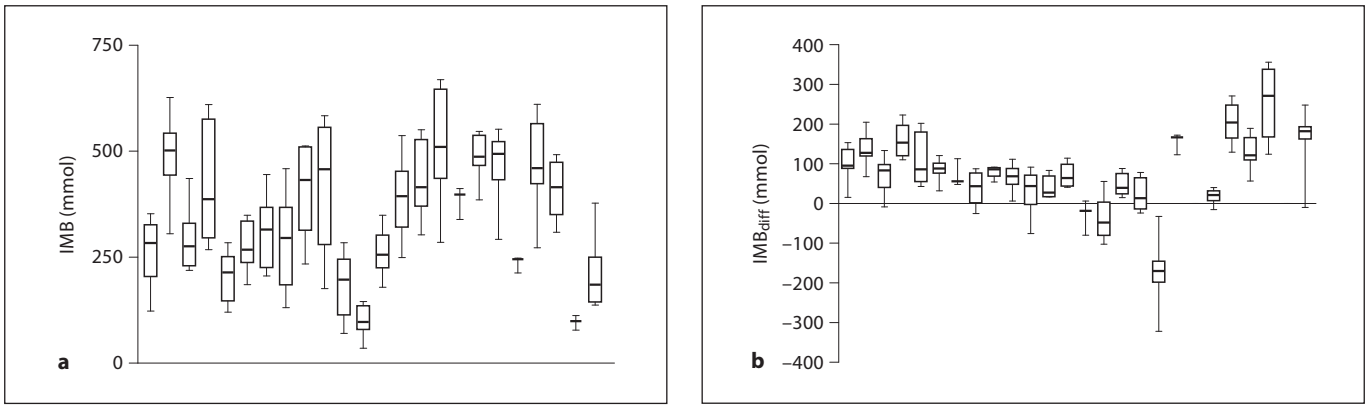

Fig. 1. Inter- and intrapatient variation in total IMB (**a**) and IMB_{diff} (**b**) over the study period in 24 patients.

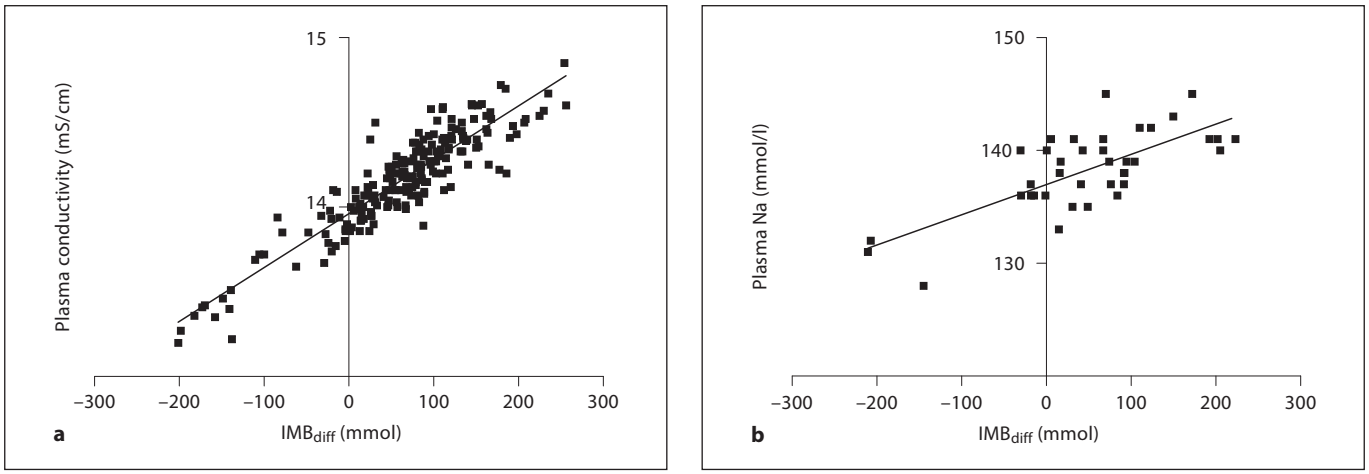

Fig. 2. Relationship between IMB_{diff} and plasma conductivity at the start of HD ($r^2 = 0.82$) (**a**) and plasma sodium concentration at the start of HD ($r^2 = 0.6$) (**b**). $p < 0.0001$.

Table 2. Correlations of IMB and IMB_{diff} to IDWG and BP

Parameter	Mean	SEM	Correlation to IMB	p value	Correlation to IMB_{diff}	p value
HD MAP, mm Hg						
Before	101.9	1.4	−0.06	0.45	−0.06	0.48
After	101.4	5.2	0.03	0.73	−0.04	0.61
IDWG, kg	1.9	0.11	0.57	<0.01	0.62	<0.01
IDWG/DW, %	2.8	0.06	0.77	<0.01	0.81	<0.01

Spearman's coefficient. MAP = Mean arterial pressure. IDWG/DW refers to IDWG as a percentage of dry weight.

from 138.8 ± 0.43 mmol/l (range, 137.9–139.7) to 134.8 ± 0.28 mmol/l (range, 134.8–136). Only 3 patients received treatments over the study period that resulted in an increase in plasma conductivity and sodium concentration. They had negative IMB_{diff} values, reflecting a positive dialysate to plasma sodium concentration gradient. Plasma sodium measurements correlated well with plasma conductivity measured by ionic dialysance (fig. 4).

There was no significant association of IMB with systolic, mean or diastolic BP either before or after dialysis. There was a significant correlation of IMB and IMB_{diff} with IDWG, whether expressed in absolute terms or relative to dry weight (table 2).

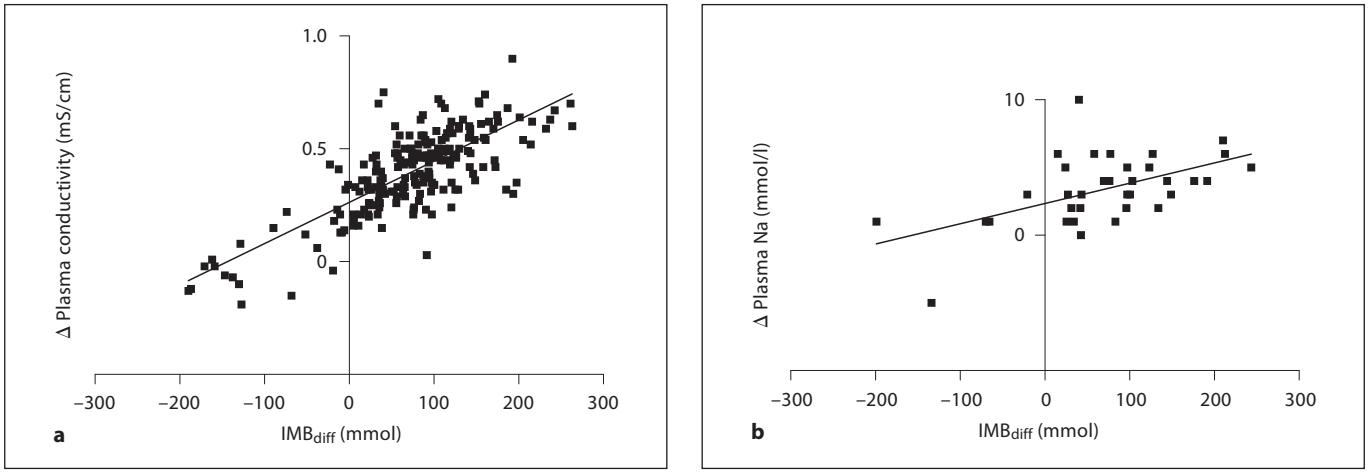

Fig. 3. Relationship between IMB_{diff} and Δ plasma conductivity from start to finish of HD ($r^2 = 0.7$) (**a**) and Δ plasma sodium concentration ($r^2 = 0.5$) (**b**). $p < 0.0001$.

There were no significant associations of IMB with total reductions in relative blood volume or intradialytic hypotensive episodes. We divided the data into after weekend days (Monday and Tuesday) against the other days and found no significant differences for all variables of interest including IDWG, pre- and post-dialysis plasma [Na], IMB, and all components of BP (non-parametric Wilcoxon test).

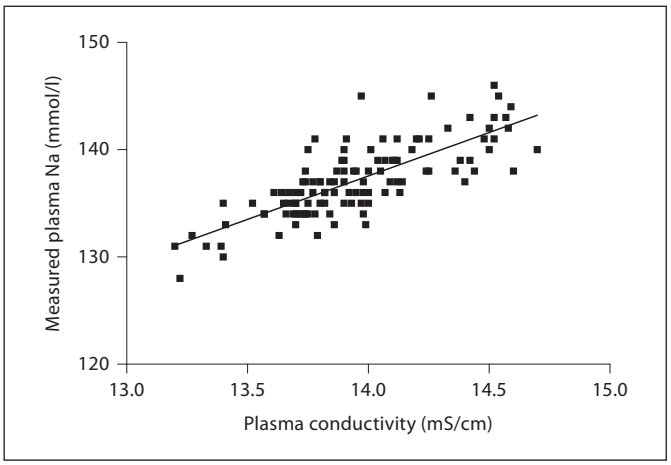

Fig. 4. Relationship between plasma conductivity and plasma sodium measurements ($r^2 = 0.6$). $p < 0.0001$.

Discussion

The aim of this study was to further evaluate the use of online conductivity monitoring to study sodium mass balance in chronic HD patients. The resultant data can best be divided into three separate, but interrelated strands. Firstly, we have demonstrated a high degree of between-patient variability in a surrogate marker of sodium mass balance (IMB) in contrast to a low degree of within-patient variability. Such a finding suggests that individualised dialysate sodium concentration would be both desirable and possible. Secondly, we have confirmed the importance of predialysis plasma sodium concentration in influencing diffusive sodium movements. Thirdly, we have demonstrated a relationship between diffusive sodium movement and the difference in plasma conductivity observed over a given HD treatment session. This may have implications for the prescription of a specific amount of desirable sodium removal. Measurement of IMB confirmed at least some sodium removal in all patients. The level of removal was highly variable between patients. When considering IMB_{diff}, the same pattern of variability was noted; however, 3 out of 24 patients had values suggesting net movement of sodium into their circulation. This level of variability has not been directly observed previously. A 2002 study by Moret et al. [21] demonstrated far less pronounced variability in IMB. This was a 13-patient study with a significant proportion having HD twice per week, with treatment times ranging from 180 to 270 min. Seven of the 13 patients had significant residual renal function and the contribution of

this to sodium mass balance was not quantified. We observed interpatient variability in IMB nearly twice as large as within patient. This is consistent with reported observed interpatient variability in plasma sodium concentrations. Gotch et al. [24] studied predialysis plasma sodium concentrations over a protracted period. Plasma sodium concentration varied from 132 to 144 mmol/l between patients, but varied by less than 2 mmol/l within individual patients. The stability of this set point and its relation to IDWG and hypertension has more recently been confirmed [25, 26]. This further supports a rationale for individualisation of the dialysate sodium prescription [27].

The distinction between sodium mass balance attributable to convection with ultrafiltration and by diffusive processes has been subject to further study, both in terms of theoretical modelling and observation. Mathematical predictions of sodium mass balance in a two-compartment model with dialysate sodium of 140 mmol/l estimate that diffusion contributes around 30 mmol of sodium removal in a 60-kg individual [28]. Both the overall values and relative contributions to total sodium removal, available from diffusion, are consistent with our data. Moret et al. [21] also used IMB measurement to study sodium removal using a variety of dialysate sodium concentrations (including 140 mmol/l). In this study, the patients were initially dialysed without ultrafiltration for 1 h during which they found a mean removal of around 30 mmol. It is difficult to use these data to estimate the contribution of diffusion to sodium mass balance over a 4-hour dialysis session as the second period of ultrafiltration was not assessed, but even a crude assumption of a linear rate of removal approximates to 120 mmol. This is of the same order as our estimate of a mean of 97 mmol for IMB_{diff} over 4 h of dialysis with a fixed ultrafiltration rate. Our derivation of IMB_{diff} would appear to be a reasonable approach to gain some further insight into the effects of dialysate sodium concentration on sodium mass balance. IMB_{diff} was strongly correlated with both predialysis plasma conductivity and plasma sodium concentration. This is in keeping with previous experimental and theoretical data [14, 29]. It has already been suggested that dialysate sodium concentration should be tailored to predialysis plasma sodium concentration in order to optimise diffusive removal [27, 30]. It should be noted that the observed levels of correlation throughout our study were generally higher when plasma conductivity, rather than plasma sodium concentration, was considered. This may well be due to a relative lack of precision with respect to plasma sodium concentration measurement [31].

We also demonstrated negative IMB_{diff} (sodium loading) in only 3 out of 24 patients. The low proportion of patients with negative IMB_{diff} despite a dialysate sodium of 140 mmol/l is not surprising, as the patients had low levels of comorbidity, no diabetes and were not prone to intradialytic hypotension. Crucially, very few patients were hyponatraemic with only 4 patients having a predialysis plasma sodium of <135 mmol/l (fig. 4), so there was a very low risk of negative IMB_{diff}. Moreover, we did not demonstrate an association between IMB and predialysis hypertension. We can speculate that a correlation would be masked by the use of antihypertensive medication in those patients with higher sodium loads. The relationship between sodium and BP in HD patients is more complicated than mere volume expansion. Previous models of sodium kinetics assume a two-compartment model, but Titze [17] has recently proposed an alternative three-compartment model by showing that sodium can accumulate in the vascular wall without volume expansion, which might explain the lag in improved BP control seen after dry weight reduction in patients treated with long-slow HD [17, 32, 33].

There was a correlation between both diffusive and total IMB and IDWG ($r = -0.57$ and -0.62, respectively; $p < 0.01$). There was also a good correlation between the difference in plasma conductivity between the start and end of dialysis (fig. 3). This suggests a theoretically robust strategy to ensure an individualised isonatric dialysis treatment. Such an approach requires the relative contributions of convection with ultrafiltration and diffusion to be recognised and independently modulated. The removal of sodium with the ultrafiltration volume is, from a physician's point of view, a largely passive process. It is determined by the level of prescribed fluid removal and therefore does not offer an opportunity for independent tailoring of sodium removal. To ensure full and adequate removal of ingested sodium, it is necessary to know the amount of ingested sodium (and insensible loss ± any effect of residual renal function). The difference between sodium ingested and sodium removed by (essentially hypotonic) ultrafiltrate would determine the degree of diffusive loss required (within the limits of cardiovascular tolerability). The ability to improve diffusive sodium removal by a lower end dialysis plasma conductivity might allow greater control over sodium balance, with the majority still due to ultrafiltration. This desired drop in plasma conductivity might be brought about by a variety of approaches. The ideal approach would be to directly prescribe a desired end dialysis plasma conductivity. This is possible by the use of a commercially available system

(Diacontrol®, Hospal). This system utilises software with sodium kinetic modelling to automatically control dialysate sodium conductivity in a biofeedback loop, to deliver a physician-prescribed end dialysis plasma conductivity. Such a system avoids continuous exposure to a persistently hypotonic dialysate [30]. Our previous study of the Diacontrol system did not show reduction in IDWG, and we attributed this to the fact that Diacontrol limits how low the desired end plasma conductivity and therefore effective sodium concentration can be set [34]. Recent work by Manlucu et al. [35] used the same Diacontrol system to achieve a stepwise reduction in postdialysis plasma conductivity from 14.0 to 13.5 mS/cm. They showed an almost identical relationship between plasma conductivity and measured plasma sodium concentration as in the current study, whilst achieving a 98 mmol increase in sodium removal estimated by IMB and a significant reduction in IDWG, BP and extracellular volume expressed as a percentage of total body water [35]. Not all centres have the availability of the Diacontrol system. In the absence of such a system, a similar result might be achieved by serial reduction in fixed dialysate sodium concentration, performed in combination with empirical observation of IMB and end plasma conductivity, until the desired reduction is achieved. The lack of intrapatient variability of both sodium removal and plasma sodium concentration suggests that such an approach might be feasible. De Paula et al. [36] propose that dialysate sodium be individualised according to the formula plasma [Na] $\times$ 0.95, where [Na] is sodium concentration measured by indirect ion-selective electrode and based on a mean of 3 values. Such an approach led to improved IDWG and BP control in their study of 27 patients [35, 36].

The limitations of this study are that it is a small sample size and the conclusions may not be applicable to a dialysis population with greater comorbidity. Though this has previously been reported, we did not perform a validation of IMB as a measure of sodium mass balance by direct concentration measurement of the spent dialysate. Since conductivity monitoring cannot distinguish between ion types, this would have allowed us to quantify for the influence of the minor cations such as potassium, calcium and magnesium. Subsequently, the calculated sodium balance may be erroneous in individuals, particularly those with the highest predialysis potassium levels. The use of direct rather than indirect potentiometry for all plasma sodium concentration measurements would more directly reflect sodium activity and potentially reduce measurement errors. Another limitation is the use of a linear model for the time evolution of plasma conductivity (see online suppl. appendix 1), which allowed an estimate of the relative contributions of ultrafiltration and diffusion to sodium mass balance. A more sophisticated approach might be to derive an exponential function to account for the likely change in dialysate to plasma sodium gradient with time, which a larger sample size might allow.

In conclusion, the use of online conductivity monitoring to study sodium mass balance would appear to be both feasible and useful in individual patients. This study supports the notion that using a fixed rather than individualised dialysate sodium prescription leads to a wide range of sodium removal with potentially unrecognised sodium loading in patients, particularly those who are hyponatraemic. Online conductivity monitoring can be utilized as part of a variety of proposed strategies to enable the delivery of individualised and isonatric HD. Further study is required to explore the utility of such strategies, which may be crucial in reducing IDWG and HD-induced cardiac injury.

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