Altering plasma sodium concentration rapidly changes blood pressure during haemodialysis

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ABSTRACT

Background. Plasma sodium is increased following each meal containing salt. There is an increasing interest in the effects of plasma sodium concentration, and it has been suggested that it may have direct effects on blood pressure (BP) and possibly influences endothelial function. Experimental increases of plasma sodium concentration rapidly raise BP even when extracellular volume falls.

Methods. Ten patients with end-stage renal failure established on haemodialysis were studied during the first 2 h of dialysis without fluid removal during this period. They were randomized to receive haemodialysis with (i) dialysate sodium concentration prescribed to 135 mmol/L and (ii) 145 mmol/L in random order in a prospective, single-blinded crossover study. BP measurements and blood samples were taken every 30 min.

Results. Pre-dialysis sitting BP was 137/76 ± 7/3 mmHg. Lower dialysate sodium concentration (135 mmol/L) reduced plasma sodium concentration [139.49 ± 0.67 to 135.94 ± 0.52 mmol/L (P < 0.001)], whereas plasma sodium concentration was not altered by higher dialysate sodium (145 mmol/L) (140.17 ± 0.66 mmol/L at baseline to 140.72 ± 0.43 mmol/L at 120 min). Systolic BP was lower with dialysate sodium concentration 135 mmol/L [area under the curve (AUC) 15823.50 ± 777.15 (mmHg)min] compared with 145 mmol/L [AUC 17018.20 ± 1102.17 (mmHg)min], mean difference 1194.70 ± 488.41 (mmHg)min, P < 0.05. There was a significant positive relationship between change in plasma sodium concentration and change in systolic BP. This direct relationship suggests that a fall of 1 mmol/L in plasma sodium concentration would be associated with a 1.7 mmHg reduction in systolic BP (P < 0.05).

Conclusions. The potential mechanism for the increase in BP seen with salt intake may be through small but significant changes in plasma sodium concentration.

INTRODUCTION

Evidence suggests that plasma sodium concentration might have a role in determining blood pressure (BP). This concept was explored mostly in the 1970s with animal and epidemiological studies, but it was then largely forgotten. A positive relationship between plasma sodium concentration and BP was described in two large epidemiological studies, but this has not been a universal finding [1–3]. The relationship has also been reported in an analysis of prospective interventional studies where salt intake was changed [4]. Experimental studies in animal models have utilized dialysis as a means of manipulating both plasma sodium concentration and extracellular volume [5–7]. One such study, in rats on peritoneal dialysis, found that BP was higher when plasma sodium concentration was increased, irrespective of extracellular volume status [7]. Another study used haemodialysis to tightly control plasma sodium concentration in sheep. When plasma sodium concentration was increased by 20% and extracellular volume was tightly controlled, arterial BP increased [6].

In clinical practice, the concentration of dialysate sodium can be altered over a haemodialysis session. High dialysate sodium concentrations have been prescribed to improve cardiovascular stability during haemodialysis and reduce the side effects associated with rapid ultrafiltration [8, 9]. More recently, lower plasma dialysate sodium has been associated with reduced inter-dialytic fluid intake, which is thought to be a result of lower plasma sodium concentration and hence reduced thirst [10].
The aim of this study was to investigate the effects of acute changes in plasma sodium concentration on BP, by altering dialysate sodium concentration in individuals on haemodialysis and by controlling extracellular volume. We measured the effects of these changes during isovolaemic haemodialysis, i.e. no fluid removal in 10 stable haemodialysis patients.

**Materials and Methods**

Study participants were recruited from a population of patients with end-stage kidney disease receiving outpatient haemodialysis at a regional renal unit. Ten stable haemodialysis patients maintained on thrice weekly maintenance haemodialysis for more than 3 months with a mean age of 60.9 ± 5.1 years provided written informed consent (Table 1). The protocol was approved by the Local Research Ethics Committee and followed local institutional guidelines (LREC Approval Number: 06/Q0803/180). Causes of end-stage renal failure were: diabetic nephropathy (4); renovascular hypertension (2); adult polycystic kidney disease (1); chronic glomerulonephritis (1); chronic pyelonephritis (1); unknown (1). Six patients took antihypertensive medication made up of a combination of ACE inhibitors or ARBs (4), β-blockers (3), calcium channel blockers (2) and diuretics (1). Antihypertensive medication was withheld on the day of dialysis.

Using a prospective, randomized single-blinded crossover design, patients were studied on two separate haemodialysis sessions, 1 week apart, ideally on the same day of the week, with each subject used as their own control. Dry weight was set by the treating physician prior to starting the study and this physician was not involved in the running of the study. No change in medication, dry weight and haemodialysis prescription was made during the study. Patients were weighed before starting haemodialysis. Initial BP measurements were taken 5 min prior to starting dialysis (Time 0) and repeated every 30 min during the study period (30, 60, 90 and 120 min). BP was measured by a validated oscillometric technique (Omron 705CP) and was taken three times at 2 min intervals. The mean of the last two measurements was used in the analysis. Where arteriovenous fistula or grafts were used for access for haemodialysis, BP measurements were taken from the other arm. Cardiac indices were measured using transthoracic electrical bioimpedance cardiography (BioZ.com) prior to starting dialysis and repeated every 30 min during the study period [11]. Blood samples for the measurement of sodium, potassium, urea, creatinine, osmolality, haemoglobin and haematocrit were drawn from the haemodialysis circuit at cannulation and then at 30 min intervals over the 2-h study period. Dialysate sodium concentration was measured from the dialysate sample and not from conductivity data. Sodium concentration in blood and dialysate samples was measured using indirect ionometry by autoanalyser (ADVIA 2400 Chemistry System, IL, USA) with a coefficient of variation of 0.65%. Osmolality was measured by freezing point depression with a CV of 0.55% (Advanced™ Micro Osmometer Model 3300, Advanced, Inc., MA, USA).

<table>
<thead>
<tr>
<th>Table 1. Baseline demographic and laboratory parameters of patients</th>
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<tr>
<td><strong>Age (years)</strong></td>
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<td><strong>Male/female (n)</strong></td>
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<td><strong>Sitting BP (n)</strong></td>
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<td><strong>Haemoglobin (g/dL)</strong>*</td>
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<td><strong>Parathyroid hormone (pmol/L)</strong>*</td>
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<td><strong>Urea reduction ratio (%)</strong>*</td>
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<td><strong>Dry weight (kg)</strong></td>
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<tr>
<td><strong>Pre-dialysis weight (kg)</strong></td>
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<tr>
<td><strong>Sitting BP</strong></td>
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<tr>
<td><strong>Dialysate Na (mmol/L)</strong></td>
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<tr>
<td><strong>Blood flow (mL/min)</strong></td>
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<td><strong>Arterial pressure (mmHg)</strong>*</td>
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<td><strong>Venous pressure (mmHg)</strong>*</td>
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<td><strong>Sodium (mmol/L)</strong></td>
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<td><strong>Urea (mmol/L)</strong></td>
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<td><strong>Creatinine (µmol/L)</strong></td>
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<td><strong>Osmolality (mOsmol/L)</strong></td>
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<td><strong>Haematocrit</strong></td>
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</table>

Values are presented as mean and SEM. The urea reduction ratio is calculated as (U_{pre} - U_{post})100/U_{pre}.

*P < 0.05.

**P < 0.001, Na 135 mmol/L versus Na 145 mmol/L.

Two different haemodialysis prescriptions were used in the first 2 h of haemodialysis: the prescribed dialysate sodium concentration was set (i) at 135 mmol/L and (ii) at 145 mmol/L. The patients received treatments in random order. No fluid was removed by ultrafiltration until the end of the study period. When the study was completed, patients received 2 h
haemodialysis with a dialysate sodium concentration prescribed to 138 mmol/L and ultrafiltration as considered appropriate by the haemodialysis medical team.

**Dialysis methods**

Haemodialysis was delivered using biocompatible Fresenius FX series medium or high flux dialysers (Fresenius 5008, Fresenius FMC, Germany) programmed to provide a dialysis flow rate of 500 mL/min and a dialysate temperature of 37°C. Standard bicarbonate-buffered dialysate concentrate (Fresenius 335, Fresenius FMC, Germany) was used to yield a dialysis fluid containing the following concentrations: bicarbonate 34 mmol/L, glucose 5.5 mmol/L, calcium 1.26 mmol/L and potassium 2.0 mmol/L. Blood flow was between 200 and 350 mL/min. All individuals received tinzaparin 2500U as anticoagulation each dialysis session.

**Statistical analysis**

Results are reported as mean ± standard error of the mean (SEM). We calculated the area under the curve (AUC) for each analyte for each patient separately and compared the mean AUC between the two dialysate sodium concentrations (135 mmol/L and 145 mmol/L) using paired Student’s t-tests. In addition, for measurements of osmolality, repeated measure analysis of variance (ANOVA), corrected for multiple comparisons using Bonferroni correction, was used to compare each time point with values and, where significant differences were found, paired measurements were compared using paired Student’s t-tests.

To study the relationship between plasma sodium concentration and BP, we calculated the regression coefficient using linear regression analysis between change in plasma sodium concentration and change in BP for each patient separately. We then calculated the pooled regression coefficient using the random effects model. The null hypothesis was rejected at P-values of less than 0.05. Data were analysed using SPSS for Windows, Rel. 15.0.0. 2006. (SPSS, Inc., Chicago, IL, USA).

**RESULTS**

Baseline demographical and clinical characteristics are presented in Table 1. Pre-haemodialysis sitting BP measured 137/76 ± 7/3 mmHg. Baseline plasma measurements and urea reduction ratio were within the standards set by the Renal Association for good clinical practice in haemodialysis (Table 1) [12]. With the exception of a raised potassium concentration before haemodialysis with dialysate sodium concentration 135 mmol/L, the biochemical and haemodialysis characteristics at the start of the study were similar at baseline on both study visits (Table 1). Measured dialysate sodium concentrations were in keeping with the prescribed dialysate sodium concentrations.

**Changes in plasma sodium concentration**

Haemodialysis with a prescribed dialysate sodium concentration of 135 mmol/L lowered plasma sodium concentration from 139.49 ± 0.67 mmol/L to 135.90 ± 0.52 mmol/L at 120 min (Figure 1). Haemodialysis with a prescribed dialysate sodium concentration of 145 mmol/L did not alter plasma sodium concentration from baseline values (baseline: 140.17 ± 0.66 mmol/L; 120 min: 140.72 ± 0.43 mmol/L). The AUC when dialysate sodium concentration was prescribed at 135 mmol/L was consistently lower than when dialysate sodium concentration was 145 mmol/L [dialysate Na 135: 16455.3 ± 43.6(mmol/L)min; dialysate sodium 145: 16841.5 ± 50.34(mmol/L)min; mean difference 386.2 ± 22.3 (mmol/L)min; P < 0.001]. The maximum difference in plasma sodium concentration was 4.78 ± 0.30 mmol/L at 120 min.

**Changes in BP**

Systolic BP fell by 9 ± 3 mmHg with dialysate sodium concentration of 135 mmol/L, from 136 ± 6 mmHg at baseline to 127 ± 7 mmHg at 120 min (Figure 2). Haemodialysis with dialysate sodium concentration 145 mmol/L did not alter systolic BP. For systolic BP, the AUC was 15823.50 ± 777.15 (mmHg)min with dialysate sodium concentration of 135 mmol/L and 17018.20 ± 1102.17 (mmHg)min with dialysate sodium concentration of 145 mmol/L; mean difference 1194.70 ± 488.41 (mmHg)min, P < 0.05. There was no significant difference in the effects on diastolic BP, with AUC 8994.75 ± 406.11 (mmHg)min with dialysate sodium concentration of 135 mmol/L and 8952.75 ± 590.61 (mmHg)min with dialysate sodium concentration of 145 mmol/L; mean difference 42 ± 268.61 (mmHg)min.

**The relationship between plasma sodium concentration and BP**

To examine the relationship between plasma sodium concentration and BP, we calculated the regression coefficient using linear regression analysis between the change in plasma sodium concentration from baseline and the change in BP from baseline at each time point. This analysis was performed for each patient separately. We then calculated the pooled regression coefficient using the random effects model. There was a significant positive relationship between change in plasma sodium concentration and change in systolic BP,
indicating the lower the plasma sodium, the lower the systolic BP. It was estimated that a 1 mmol/L fall in plasma sodium concentration is associated with a 1.7 mmHg fall in systolic BP (95% CI: 0.08–3.33, P < 0.05) (Figure 3). There was no significant relationship between change in diastolic BP and change in plasma sodium concentration [effect size 0.16 (−1.15 to 1.48, P = 0.81)].

**Effect of altering dialysate sodium concentration on other variables**

Plasma osmolality initially fell in both visit but when dialysate sodium concentration was 135 mmol/L, plasma osmolality was consistently lower than when dialysate sodium concentration was 145 mmol/L (Figure 4). This difference did not reach significance when using AUC to evaluate the effect on plasma osmolality, dialysate sodium 135 mmol/L 35419.5 ± 443.10 (mOsm)min; dialysate sodium concentration 145 mmol/L 35805.0 ± 224.64 (mOsm)min; mean difference 385.5 ± 493.69 (mOsm)min, P = 0.45. However, using the repeated measures ANOVA, this difference was significant with a mean difference of 12.0 ± 1.1 mOsmol/L at 120 min, P < 0.001.

There was no significant difference in plasma potassium concentration between dialysate sodium concentrations. AUC with dialysate sodium concentration 135 mmol/L was 488.68 ± 11.3 (mmol)min and with dialysate sodium concentration 145 mmol/L was 476.50 ± 16.0 (mmol)min; mean difference 12.18 ± 11.68 (mmol)min. Urea was not significantly different between the two haemodialysis sessions with AUC 1539.84 ± 94.8 (mmol)min with dialysate sodium concentration 135 mmol/L and 1485.5 ± 122.5 (mmol)min with dialysate sodium concentration 145 mmol/L; mean difference 54.34 (mmol)min, P = 0.587. The AUC of haematocrit was 34.5 ± 4.4 (%)min with dialysate sodium concentration of 135 mmol/L and was 38.2 ± 1.3 (%)min with dialysate sodium concentration 145 mmol/L. The mean difference was 3.73(%)min. This difference was not significant. Cardiac indices were not significantly different at baseline and were not significantly altered by dialysate sodium concentration (Table 2).

**DISCUSSION**

In this study, we used haemodialysis to alter plasma sodium concentration while keeping extracellular volume constant. This has allowed careful description of the effect of plasma sodium concentration on BP. Systolic BP altered rapidly with reduction in plasma sodium concentration. The observed differences in systolic BP between dialysate sodium concentrations reached a difference of 8 ± 3 mmHg within 1 h and a larger difference of 12 mmHg at 2 h. In addition, there was a significant direct relationship between plasma sodium concentration and systolic BP.

Lower dialysate sodium concentration improves BP control in patients undergoing maintenance haemodialysis, primarily through effects on inter-dialytic weight gains and thirst [13–15]. In these studies of sustained alterations in dialysate sodium concentration, systemic vascular resistance fell when
Elevated plasma sodium concentration may also have pressor effects through increases in cerebrospinal fluid sodium concentration, with activation of osmoreceptors in third ventricle periventricular tissues and overactivity of the hypothalamic angiotensin II system giving rise to increased sympathetic outflow [4, 20, 21]. However, given that these changes occur over a longer period of time (1–2 weeks), it is unlikely that there were significant changes in cerebrospinal fluid sodium concentration that could account for the rapid changes in BP seen in this study [4].

Our study had several limitations. Haemodialysis with a higher prescribed dialysate sodium concentration did not increase plasma sodium concentration. Sodium transport across dialysis membranes by diffusion is complicated by the significant and differing percentages of sodium available for diffusion [22]. Although it is known that there is no net diffusive transport between blood and dialysate when the dialysate sodium concentration is ±2 mmol/L higher than plasma sodium concentration. This difference in concentrations before diffusion can be larger than theoretically assumed due to protein coating of the dialysis membrane [23]. Other investigators have shown a 5 mmol/L difference between plasma sodium and dialysate sodium concentration was required for diffusive sodium transport [8, 22, 24, 25]. Influx of sodium from the dialysate is limited to those instances where supraphysiological dialysate sodium concentrations are utilized, or in patients with low pre-dialytic plasma sodium concentrations [24]. Additionally, it is possible that the short length of the study played a role in limiting diffusion which is governed by the availability of free ions, i.e. sodium, that is not bound to anions [24] and the amount of free sodium [26]. It is important to note that haemodialysis took place at 37°C. Results from this study may not be applicable with cooler dialysate.

Dialysate preparation was achieved using a 3-stream proportioning system in combination with 8.4% bicarbonate concentration at a ratio of 1 part A/335 + 32.775 parts purified water + 1.225 parts NaHCO3 8.4%. The change in dialysate sodium concentration is achieved by small alterations in this ratio. Clearly, as potassium, calcium and magnesium are also contained in the acid concentrate, altering the relative delivery rate of acid concentration is likely to result in changes in the final concentration of these salts. While we did not measure calcium or magnesium concentration, there was no significant difference in the plasma concentration of potassium between the two haemodialysis sessions. Additionally the alterations in concentration are likely to be small, given that the majority of the concentrate is made up of sodium chloride. Thus, we believe that these small changes are unlikely to a major contributor to the findings of this study.

The patients in this study had a complexity of factors which can influence BP responses, including hypertension, diabetes, secondary hyperparathyroidism and erythropoietin supplementation. Using a crossover design minimizes the potential confounding effects of these factors. The higher potassium concentration seen prior to haemodialysis with dialysate sodium concentration 135 mmol/L may be attributable to the longer duration between dialysis sessions in this group.

### Table 2. Cardiac indices with dialysate sodium 135 mmol/L and dialysis sodium 145 mmol/L

<table>
<thead>
<tr>
<th>Dialysis sodium concentration</th>
<th>135 mmol/L</th>
<th>145 mmol/L</th>
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<tbody>
<tr>
<td>Pre HD CI (L/min/1.73 m³)</td>
<td>3.6 ± 0.5</td>
<td>4.2 ± 0.4</td>
</tr>
<tr>
<td>2 h CI (L/min/1.73 m³)</td>
<td>3.9 ± 0.39</td>
<td>4.1 ± 0.32</td>
</tr>
<tr>
<td>Pre HD SV (mL)</td>
<td>54.1 ± 7.5</td>
<td>62.4 ± 5.9</td>
</tr>
<tr>
<td>2 h SV (mL)</td>
<td>57.5 ± 6.1</td>
<td>62.5 ± 5.7</td>
</tr>
<tr>
<td>Pre HD SVRI (dyne/s/cm²/1.73 m³)</td>
<td>2501 ± 515</td>
<td>1912 ± 260</td>
</tr>
<tr>
<td>2 h SVRI (dyne/s/cm²/1.73 m³)</td>
<td>2138 ± 344</td>
<td>1709 ± 177</td>
</tr>
</tbody>
</table>

All values are mean ± SEM. CI, cardiac index; SVRI, systemic vascular resistance index; SV, stroke volume. There was no significant difference between the values at baseline or at 2 h.
This study has used haemodialysis as a means of demonstrating that a reduction in plasma sodium concentration is associated with a rapid fall in systolic BP. We also found that there was a significant direct relationship between plasma sodium concentration and BP. This finding corroborates observations in hypertensive and normotensive individuals [18, 19].

**Perspectives**

The results of this small, but carefully controlled study are interesting and potentially important. We have explored the dynamic relationship between plasma sodium and BP. At present it is not clear how habitual consumption of salt increases BP, but it is possible that the effect is mediated through transient changes in plasma sodium concentration. How salt increases BP has remained a fundamental but unanswered question for decades. The experimental model used in our study is a safe, acceptable and reproducible method and could be utilized for further studies to investigate the mechanisms underlying the dynamic BP responses to salt.

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**CONFLICT OF INTEREST STATEMENT**

None declared.

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12. UK Renal Association Clinical Practice Guidelines Committee: Module 3a Haemodialysis in, 2007

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