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

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Abstract

Background. Sodium profiling improves haemodynamic 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 SP (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.

Keywords: Hypertension; plasma conductivity; sodium profiling

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/C223 module) continuous adjustments of dialysate conductivity in response to measured changes in BV [2]. 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 PC [3–5]. 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 studies [3–10], 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 period [6–9]. 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 session [11], 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

12 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 1. The study was approved by the Ethics committee of the Maxima Medical Centre. All patients gave written informed consent.

### Design

All patients were treated with standard HD treatment (DC 140 mmol/l), a linear decreasing sodium profile (DC 15.0 → 14.0 mmol/l), 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, BV-controlled feedback–PC-controlled feedback–standard dialysis–sodium profile.

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 1. Polysulphone (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 = [(Q_{d_{in}} × C_{d_{in}})Q_{d_{out}} × C_{d_{out}}] × 10 × time (min). Q_{d_{out}} and Q_{d_{in}} are dialysate flow at, respectively, outlet and inlet; C_{d_{out}} and C_{d_{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 C_{d_{out}} and C_{d_{in}} according to the formula. PC = \left[ C_{d_{out}} - (1 - D/QD) × C_{d_{in}} \right] / (D/QD). D is assessed every 30 min by measuring the increase in C_{d_{out}} after a temporary increase in C_{d_{in}} by 1 mS/cm according to the formula D = Q_{d} × 1 / (1 - (C_{d_{out}}2 - C_{d_{out}}1) / (C_{d_{in}}2 - C_{d_{in}}1)). 1 and 2 indicate, respectively, the measurements before and after the temporary increase in C_{d_{in}} [4,11,12].

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Age</th>
<th>71 ± 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>6/4</td>
</tr>
<tr>
<td>Time on dialysis (months)</td>
<td>24.1 ± 17.7</td>
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<tr>
<td>Duration of dialysis (hours)</td>
<td>3.9 ± 0.5</td>
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<tr>
<td>Diabetes mellitus</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Congestive heart failure (NYHA III)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Use of ACE inhibitors</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Kt/V (single pool)</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>38.2 ± 3.8</td>
</tr>
</tbody>
</table>

Relative blood volume

BV was measured continuously by continuous optical assessment of changes in haemoglobin during the dialysis session (Haemoscan®, Hospal-Gambro) [13].
Description of the feedback modules

BV-controlled feedback (Hemocontrol®; Hospal-Gambro), described in detail elsewhere [6], 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, 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 HD [6]. The control variables consist of the set ultrafiltration rate (UFR) and 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.

Serum sodium

Serum sodium was assessed by indirect 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%.

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 to <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/cm [11], 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 IMB [11], 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 for 440 sessions were analysed.

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 1 and Table 2). Post-dialytic PC was significantly lower during PC-controlled feedback compared to the other manoeuvres.

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 sessions 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 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 \((n = 80)\). \((248 \pm 98 \text{ vs } 416 \pm 174 \text{ mmol/l}; P < 0.001)\) despite comparable ultrafiltration volume \((2.0 \pm 0.7 \text{ vs } 2.0 \pm 1.1 \text{ kg})\).

**Fig. 1.** Pre- and post-dialytic PC levels during the different modalities. Covered boxes indicate 25–75% with median value; captured bars indicate the range of data. Dots indicate outliers. Both pre- and post-dialytic PC were significantly lower 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 2.**

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>BV-feedback</th>
<th>PC-feedback</th>
<th>Sodium profile</th>
</tr>
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<tbody>
<tr>
<td>Pre-dialytic PC (mS/cm)(^a)</td>
<td>14.22 ± 0.20</td>
<td>14.22 ± 0.17</td>
<td>14.14 ± 0.22</td>
<td>14.37 ± 0.14(^b)</td>
</tr>
<tr>
<td>Post-dialytic PC (mS/cm)(^a)</td>
<td>14.11 ± 0.20(^c)</td>
<td>14.11 ± 0.10(^c)</td>
<td>14.03 ± 0.04(^b)</td>
<td>14.33 ± 0.09(^b)</td>
</tr>
<tr>
<td>DC (mS/cm)(^a)</td>
<td>14.06 ± 0.06</td>
<td>14.23 ± 0.04(^b)</td>
<td>14.03 ± 0.12</td>
<td>14.42 ± 0.05(^b)</td>
</tr>
<tr>
<td>Ionic mass removal (mmol)</td>
<td>383 ± 112</td>
<td>432 ± 80</td>
<td>370 ± 140</td>
<td>414 ± 106</td>
</tr>
<tr>
<td>IDWG (kg)</td>
<td>2.0 ± 1.0</td>
<td>2.2 ± 0.7</td>
<td>2.0 ± 0.9</td>
<td>2.1 ± 1.0</td>
</tr>
<tr>
<td>Decline in relative BV (%)</td>
<td>−6.1 ± 2.4</td>
<td>−6.6 ± 2.3</td>
<td>−6.4 ± 3.1</td>
<td>−7.4 ± 2.1</td>
</tr>
<tr>
<td>Pre-dialytic SBP (mmHg)</td>
<td>146 ± 26</td>
<td>140 ± 23</td>
<td>145 ± 19</td>
<td>144 ± 22</td>
</tr>
<tr>
<td>Nadir dialytic SBP (mmHg)</td>
<td>111 ± 22</td>
<td>108 ± 19</td>
<td>111 ± 17</td>
<td>112 ± 18</td>
</tr>
<tr>
<td>Post-dialytic weight (kg)</td>
<td>76.8 ± 14.2</td>
<td>76.1 ± 15.0</td>
<td>76.1 ± 14.8</td>
<td>76.5 ± 14.6</td>
</tr>
</tbody>
</table>

PC, plasma conductivity; DC, dialysate conductivity; IDWG, inter-dialytic weight gain; SBP, systolic blood pressure; BV, blood volume.

\(^aP < 0.05\) (ANOVA).

\(^bP < 0.001\) compared to all other treatments.

\(^cP < 0.001\) compared to pre-dialytic values.
Pooling all treatments, ionic mass removal was highly dependent upon both ultrafiltration volume ($\beta = 0.72; P < 0.001$) and the difference between predialytic plasma conductivity and dialysate conductivity ($\beta = 0.72; P < 0.001$) (Figure 2), but not on the treatment modality.

**Inter-dialytic weight gain and blood pressure and blood volume**

Neither inter-dialytic weight gain nor predialytic blood pressure differed significantly between the various treatment modalities (Table 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 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, $n = 32$ ($P = \text{NS}$). 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% ($P = \text{NS}$).

The peak systolic blood pressure did not differ between the various sessions (Table 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 predialytic PC was observed during the sodium profile, but not during BV-controlled feedback, whereas predialytic 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 interesting but somewhat cumbersome 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 conductivity [11]. 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
Conflict of interest statement. None declared.

References


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