High Dialysate Calcium Concentration May Cause More Sympathetic Stimulus During Hemodialysis


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Key Words
Heart rate variability • Hemodynamics • Autonomic nervous system • Ankle-brachial index

Abstract
Background/Aims: Acute activation of sympathetic activation during hemodialysis is essential to maintain blood pressure (BP), albeit long-term overactivity contributes to higher mortality. Low heart rate variability (HRV), a measure of autonomic nervous system activity, and abnormal ankle-brachial index (ABI) are associated with higher mortality in patients on hemodialysis. In this study, we assessed HRV and ABI pre and post dialysis in incident patients on hemodialysis using high (1.75mmol/l) and low (1.25mmol/l) dialysate calcium concentration (DCa).

Methods: HRV was measured as the ratio between low frequency and high frequency power (LF/HF). Thirty patients (age 47±16 years, 67% men) were studied in two consecutive mid-week hemodialysis sessions.

Results: Mean BP variation was positive with DCa 1.75 and negative with DCa 1.25 [4.0 (-6.0, 12.2 mmHg) vs. -3.2 (-9.8, 1.3 mmHg); p=0.050]. Reduction of ABI from pre to post HD was related to higher sympathetic activity (p=0.031). The increase in LF/HF ratio was higher with DCa 1.75 (58.3% vs. 41.7% in DCa 1.75 and 1.25, respectively, RR 2.8; p=0.026).

Conclusion: Although higher DCa is associated with better hemodynamic tolerability during hemodialysis, this occurs at the expense of increased sympathetic activity. Higher sympathetic activity was associated with a decrease of ABI during hemodialysis.
Introduction

Cardiovascular mortality risk is high in patients on maintenance dialysis, which is even higher in those starting such therapy [1]. Multiple traditional and novel cardiovascular risk factors contribute to explain why these patients exhibit increased cardiovascular death, left ventricular hypertrophy, electrolytes abnormalities, fluid overload, sleep apnea and sympathetic overactivity [2]. The latest has an important role in conventional hemodialysis (HD) sessions, by increasing peripheral arterial resistance in response to reduced intravascular volume caused by ultrafiltration. This mechanism is necessary to maintain blood pressure (BP) during HD sessions [3].

Low heart rate variability (HRV), a measure of autonomic nervous system, is associated with higher cardiovascular mortality in the setting of end-stage renal disease (ESRD) [4-6]. Albeit reduction of HRV may be related to alterations in cardiovascular structure, it is also associated with changes in hemodynamic behavior during HD [6]. Indeed, changes in HRV have been used to predict hemodynamic instability, [4] and it is also associated with left ventricular hypertrophy [7].

Ankle brachial index (ABI), another marker of mortality in patients on HD [8] is correlated to HRV in both, normal subjects [9, 10] and in patients with high cardiovascular risk [11]. The ABI, which is calculated by the division of the higher systolic BP at the ankle by the higher systolic BP at the arm, is usually assessed pre dialysis. Yet, ABI can vary during HD, so that even the classification among low, normal and high values can vary [12]. A lower ABI usually indicates peripheral artery disease, whereas an elevated ABI indicates arterial sclerosis due to a more pronounced calcification of the vessel wall. Both low and high ABI are associated with increased mortality in patients on HD [8, 13]. Since there is an interaction between the autonomic nervous system and the vascular response [14], acute changes in ABI during HD may be a result of the sympathetic response to ultrafiltration.

Given that high dialysate calcium (DCa) concentration is related to better hemodynamic tolerability during HD, we hypothesized that higher DCa might lead to a higher sympathetic activity, which may explain acute changes in ABI during HD. If true, the high mortality rate imputed to high dialysate calcium concentration [15, 16] would be partially explained by the increased sympathetic activity.

Patients and Methods

Study population

This was a prospective study that included consecutive incident patients on HD, defined as less than 30 days since the first HD session, at the Hospital das Clinicas da Universidade de Sao Paulo. Exclusion criteria were patients who had symptomatic congestive heart failure (New York Heart Association Functional Classification class III and IV), lower limb amputation or atrial fibrillation. The protocol was approved by the Local Ethical Board (#11534213.0.0000.0068), and consisted in analyses of ABI and HRV pre and post HD in two consecutives mid-week dialysis: the first with higher DCa concentration (DCa=1.75 mmol/l) and the second with lower DCa concentration (DCa=1.25 mmol/l). Between these dialysis sessions, patients underwent dialysis with DCa 1.75 mmol/l.

All dialysis sessions were performed using Fresenius 4008S machines and high flux polysulfone membranes (Fresenius Medical Care™, Bad Homburg, Germany). Blood flow was set to 350 mL/minute and dialysate flow to 500 mL/minute, duration 3:30h, schedule 3 times a week. Ultrafiltration was prescribed according to dry weight.

Laboratory blood tests were done before and after each study dialysis session using standardized techniques and included urea, hemoglobin, hematocrit, total and ionized calcium. Renin and aldosterone were measured by immunochemiluminometric and chemiluminescence methods, respectively; parathyroid hormone (PTH) was measured by eleetroquimioluminescence; n-terminal pro-brain natriuretic peptide (NT-pro BNP) was measured by enzyme immunoassay.
Ankle Brachial Pressure Index Measurement

All measurements were made in the same dialysis room with a controlled temperature (22 ± 2° C) and with patients in a sitting position with legs straight. The measurements were done using two oscillometric devices (Omron 705 CP; Omron Corp., Tokyo, Japan) simultaneously to measure the blood pressure in the upper and lower extremities, as previously described by our group [8, 12]. Cuffs were comfortably set in place, adjusted to the arm above the cubital malleolus with the cuff directed towards the brachial artery trajectory, and directed toward the trajectory of the posterior tibial artery. One oscillometric pressure reading was measured at each extremity. For those cases with error(s), a second reading was tried. In case of an arteriovenous fistula, only the contralateral limb was assessed. The same examiner in all situations performed the protocol. During the study, only raw blood pressure values were recorded and stored on a database for later ABI calculation. ABI was calculated as the ratio between the higher lower limb and upper limb systolic BP. ABI was considered low, normal and high with values <0.9, 0.9-1.3 and ≥ 1.3, respectively.

Heart rate variability measurements

We used finger beat-to-beat monitor Finometer™ (Finapress Medical Systems BV, Arnhem, The Netherlands) that recorded non-invasively the arterial pulse waves to assess HRV. The measurement was done pre and post dialysis. The same trained physician analyzed the beat-to-beat interval records with the Kubios HRV v.2.2™ Software (University of Eastern Finland, Kuopio, Finland), blinded to the exposures (Dca 1.75 or Dca 1.25). Ectopic beats were excluded from analysis, so that only normal sinus recording was used to assess HRV. As the acquisition time in each exam was short, the spectral HRV analysis was performed and the following components were used: low frequency power (LF - 0.05-0.15 Hz) and high frequency power (HF - 0.15-0.5 Hz) [17]. LF denotes sympathetic activity while HF denotes mainly the parasympathetic modulation of heart rate, and an increase in the ratio LF/HF was used as indicator of higher sympathetic activity. Finometer™ also obtained BP pre and post HD [17].

Statistical analysis

Biochemical, hemodynamic and heart rate variability variables obtained with Dca 1.75 and Dca 1.25 were compared by paired t-test or Wilcoxon test as appropriate, according to Kolmogorov-Smirnov test. Values pre dialysis were compared by student t-test or Mann-Whitney as appropriate. ABI was treated as continuous and categorical variable (increase vs. decreased from pre to post dialysis). The χ2 or Fisher exact test was used to compare nominal variables as appropriate. Data are presented as mean ± standard deviation (SD). A p value of ≤0.05 was considered significant. Analyses were performed using SPSS 20 (SPSS Inc, Chicago, IL, USA) and Prism 6 (GraphPad Software, Inc) statistical software packages.

Results

The mean age of the study population was 47 ± 16 years, 67% were men, and HD vintage was 30 (19, 40) days. The underline kidney disease was hypertensive nephrosclerosis in 27%, chronic glomerulonephritis in 17%, diabetes, lupus and polycystic kidney disease in 10% each, other diseases including pyelonephritis and multiple myeloma were found in 10%, and unknown disease in the remaining 6% of cases.

The totality of patients was hypertensive and was on medication, which included beta-blockers in 18 patients (60%), and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in 13 patients (43%). There was no change in any of these medications during the study. The mean body mass index was normal (22.9 ± 4.0 kg/m²), although two patients had values between 25 and 30 kg/m² and another two had values between 30 and 35 kg/m².

Biochemical values pre and post dialysis with DCA 1.75 and DCA 1.25 are shown in Table 1. There was no difference when comparing all biochemical values pre dialysis between DCA 1.75 and DCA 1.25. Total ultrafiltration and ultrafiltration rate were similar when comparing DCA 1.75 and DCA 1.25 (2.1 ± 0.8 vs. 2.2 ± 0.7 L and 10.2 ± 4.3 vs. 10.2 ± 4.1 ml/kg/h, respectively; NS). As expected, there was an increase in haemoglobin, hematocrit, and
a decrease in urea post dialysis, with both DCa. Total calcium increased and PTH decreased significantly after dialysis only with DCa 1.75.

As shown in Table 2, there was a decrease in systolic and mean BP while on DCa 1.25 and a slightly increase while on DCa 1.75. The delta of the systolic BP on DCa 1.75 and DCa 1.25 was 10.5 (-9.1, 18.4) and -6.5 (-19.4, 6.8) mmHg, with a tendency towards significance (p=0.079). In the same way, the delta of mean blood pressure was more positive with DCa 1.75 and more negative with DCa 1.25 [4.0 (-6.0, 12.2 mmHg) vs. -3.2 (-9.8, 1.3 mmHg); p=0.050].

Table 2. Hemodialysis impact on blood pressure and weight using high dialysate calcium concentration (DCa) 1.75 mmol/l and 1.25 mmol/l

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre HD</th>
<th>Post HD</th>
<th>Pre HD</th>
<th>Post HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>154.6 ± 33.7</td>
<td>156.0 ± 24.8*</td>
<td>157.5 ± 29.6</td>
<td>149.3 ± 29.8*</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>80.3 ± 14.1</td>
<td>80.3 ± 14.1</td>
<td>82.1 ± 15.4</td>
<td>80.4 ± 11.8</td>
</tr>
<tr>
<td>Mean blood pressure, mmHg</td>
<td>106.2 ± 19.1</td>
<td>108.1 ± 15.8*</td>
<td>107.5 ± 17.8</td>
<td>102.2 ± 17.8*</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>63.2 ± 14.7</td>
<td>61.1 ± 14.6</td>
<td>63.3 ± 14.7</td>
<td>61.1 ± 14.6</td>
</tr>
</tbody>
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Abbreviations: HD, hemodialysis; Values are expressed as mean ± SD or median (25, 75) as appropriate. * p<0.05 vs. pre HD.
Relationships between changes in ABI and changes in LF/HF, from pre to post dialysis were demonstrated in Figure 3. An increase in LF/HF, denoting higher sympathetic activity was associated with a decrease in ABI, which was observed while on high DCa (p=0.031).

Discussion

This study has given rise to some novel findings regarding sympathetic activity during HD. We have demonstrated that high DCa is associated with an increase in the LF/HF ratio, denoting higher sympathetic activity when compared to low DCa. In addition, the increased in the LF/HF ratio was associated with a decrease in the ABI. Taken together, these findings suggest that high DCa increases sympathetic activity, leading to better hemodynamic stability during HD. Sympathetic activity was also associated with an acute decrease in ABI, which clinical significance is unknown. These findings expand actual scientific knowledge, not only
by confirming the association between HRV and ABI [9-11, 14], but also by showing that this is also applicable in the setting of ESRD patients on HD. Our study was limited to incident patients on HD. This population is particularly subject to acute complications and also to higher mortality risk among all HD patients [1, 18]. It is important to understand which factors are associated with this higher mortality in order to improve medical care of these patients. After initiation of renal replacement therapy, incident patients on HD are submitted to successive high ultrafiltration rates in order to achieve the "dry weight". However, during this process, patients are subject to hypotension and cardiovascular complications, which may account to increased mortality risk. High DCa seems to be the ideal dialysate bath, as it promotes better hemodynamic stability. However, it should be considered that higher DCa might be associated with a higher sympathetic activity, decreased arterial compliance and intradialytic hypertension [19, 20]. So that, the dialysis prescription should be individualized and the routine use of high DCa should be avoided unless clinically indicated [21], since for long-term, sympathetic overactivity can lead to hypertension and unfavourable outcomes [4].

ABI is a well-established marker of mortality among HD patients [8, 13, 22]. Acute changes on ABI from pre to post dialysis are not usually reported. ABI changes during HD may either merely reflect blood pressure response to ultrafiltration or the autonomic response capacity of a patient. If the later is true, a decrease in ABI from pre to post dialysis is due to sympathetic activity. Further studies are necessary to confirm this finding, and also to check if acute changes in ABI may be related to long-term mortality in patients on HD.

The increase in the LH/HF ratio was more frequent with a DCa 1.75. One can argue that this finding is expected, and explains the better hemodynamic tolerability associated with this dialysis bath. The increase in DCa seems to be associated with an increased myocardial contractility as a result of acute increase in serum calcium [23]. The observed sympathetic overactivity that occurs with high DCa, at least thrice a week, for a patient on conventional HD, raises a concern regarding the benefit of increase DCa for a long-term.

It is plausible to consider that sympathetic overactivity in patients on HD may be a consequence of the renin-angiotensin system activation. This is due to the angiotensin II action on receptor 1, in the central nervous system, which increases systemic vascular resistance [24]. The renin-angiotensin system is activated because of the decreased intravascular volume as a consequence of the ultrafiltration process.

Our study is subject to some limitations. First, subjects were relatively young. Therefore, our study population is not representative of a global population on dialysis. Second, we have enrolled a relatively small sample size. We could partially overcome this limitation by...
studying the same patient twice, which possibly reduced this weakness. Third, there are possible other factors that could contribute to the sympathetic activity that were not taken into account while interpreting the results. In this regard, the use of beta-blockers, the most usual drug that interfere in the autonomic response did not have any impact on our results. Again, there was no change in any medication from one to another hemodialysis session analyzed in the present study. The current study has also strength in demonstrating that high DCA is accompanied by a higher sympathetic activity than low DCA. Moreover, an acute decrease in ABI during dialysis seems also represent a sympathetic stimulus.

**Conclusion**

Our findings suggest that high DCA is associated with increased sympathetic activity during hemodialysis. Higher sympathetic activity was associated with a decrease of ABI during hemodialysis. Further studies are required to determine whether reducing DCA in incident population on HD would decrease sympathetic activity, and whether this approach would bring an improvement in long-term survival.

**Disclosure Statement**

The authors of this manuscript state that they do not have any conflict of interests and nothing to disclose.

**References**