Effects of acute variation of dialysate calcium concentrations on arterial stiffness and aortic pressure waveform

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Abstract

Background. Abnormal mineral metabolism in chronic kidney disease plays a critical role in vascular calcification and arterial stiffness. The impact of presently used dialysate calcium concentration (D_{Ca}) on arterial stiffness and aortic pressure waveform has never been studied. The aim of the present study is to evaluate, in haemodialysis (HD) patients, the impact of acute modification of D_{Ca} on arterial stiffness and central pulse wave profile (cPWP).

Method. A randomized Latin square cross-over study was used to evaluate the three different concentrations of D_{Ca} (1.00, 1.25 and 1.50 mmol/L) during the second HD of the week for 3 consecutive weeks. Subjects returned to their baseline D_{Ca} for the following two treatments, allowing for a 7-day washout period between each experimental HD. cPWP, carotido-radial (c-r) and carotido-femoral (c-f) pulse wave velocities (PWV), plasma level of ionized calcium (iCa) and intact parathyroid hormone (PTH) were measured prior to and immediately after each experimental HD session. Data were analysed by the general linear model for repeated measures and by the general linear mixed model.

Results. Eighteen patients with a mean age of 48.9 ± 18 years and a median duration of HD of 8.7 months (range 1–87 months) completed the study. In post-HD, iCa decreased with D_{Ca} of 1.00 mmol/L (−0.14 ± 0.04 mmol/L, P < 0.001), increased with a D_{Ca} of 1.50 mmol/L (0.10 ±...
0.06 mmol/L, \( P < 0.001 \) but did not change with a \( \Delta c_{-f} \) of 1.25 mmol/L. Tests of within-subject contrast showed a linear relationship between higher \( \Delta c_{-f} \) and a higher post-HD \( \Delta c_{-f} \) PWV, \( \Delta c_{-f} \) PWV and \( \Delta \)mean BP (\( P < 0.001 \), \( P = 0.008 \) and \( P = 0.002 \), respectively). Heart rate-adjusted central augmentation index (Alx) decreased significantly after HD, but was not related to \( \Delta c_{-f} \). The timing of wave reflection (Tr) occurred earlier after dialysis resulting in a linear relationship between higher \( \Delta c_{-f} \) and post-HD earlier Tr (\( P < 0.044 \)). In a multivariate linear mixed model for repeated measures, the percentage increase in c-f PWV and c-r PWV was significantly associated with the increasing level of iCa, whereas the increasing level of \( \Delta MBP \) was not significant. In contrast, the percentage decrease in Tr (earlier wave reflection) was determined by higher \( \Delta MBP \) and higher ultrafiltration, whereas the relative change in Alx was inversely determined by the variation in the heart rate and directly by \( \Delta MBP \).

Conclusion. We conclude that \( \Delta c_{-a} \) and acute changes in the serum iCa concentration, even within physiological range, are associated with detectable changes of arterial stiffness and cPWP. Long-term studies are necessary to evaluate the long-term effects of \( \Delta c_{-a} \) modulation on arterial stiffness.

Keywords: arterial stiffness; calcium; haemodialysis; pulse wave profile; pulse wave velocity

Introduction
The high prevalence of cardiovascular disease among haemodialysis (HD) patients cannot be explained solely by traditional cardiovascular risk factors. More recently, arterial stiffness, as measured by carotid-femoral (c-f) pulse wave velocity (PWV), has been shown to be an independent predictor for cardiovascular morbidity and mortality in a HD population [1,2]. Physiologically, increased stiffness of the large elastic arteries leads to increased central pulse pressure (PP), cardiac workload and left ventricular hypertrophy [3–7]. The mechanism of arterial stiffness in advanced chronic kidney disease (CKD) remains poorly understood. Alteration of the vascular wall by chronic effects of hypertension, accumulation of advanced glycation end-products and abnormal mineral metabolism are some of the mechanisms that have been proposed to explain the increased arterial stiffness in CKD [8–11]. The relationship between calcium containing phosphate binders and vascular calcification has raised concern about the long-term effects of chronic positive calcium balance [12,13]. However, the concerns about calcium containing phosphate binders have overshadowed the importance of dialysate calcium concentration (\( \Delta c_{-a} \)) in the overall calcium balance. Although, DOQI guidelines recommend a \( \Delta c_{-a} \) of 1.25 mmol/L, the optimal \( \Delta c_{-a} \) could also be determined by other factors such as the use of specific phosphate binders, vitamin D or vitamin D analogues.

Although logical, the direct relationship between arterial calcification and arterial stiffness has recently been challenged [14,15]. The aim of the present study is to evaluate the impact of acute modification of calcemia, within the physiological range, on arterial stiffness, as evaluated by PWV, and on the central pulse wave profile (cPWP) in a HD population. In this experimental protocol, each subject underwent three experimental HD sessions with random allocation of \( \Delta c_{-a} \) of 1.00, 1.25 or 1.50 mmol/L.

Subjects and methods
Study design and patient population
This study took place at the Centre Hospitalier Universitaire de Québec—L’Hôtel-Dieu de Québec Hospital, over a 7-month period in 2007. This was a Latin square cross-over study using three different concentrations of \( \Delta c_{-a} \) for the second HD of the week for 3 consecutive weeks. Subjects returned to their baseline \( \Delta c_{-a} \) for the following two treatments, allowing for a 7-day washout period between each experimental HD. Each subject was randomly assigned to one of the three different sequences of \( \Delta c_{-a} \): sequence 1 (\( \Delta c_{-a} \) of 1.00, 1.25, 1.50 mmol/L), sequence 2 (\( \Delta c_{-a} \) of 1.25, 1.50 and 1.00 mmol/L) and sequence 3 (\( \Delta c_{-a} \) of 1.50, 1.00 and 1.25 mmol/L). No other parameters of the HD prescription or medication were modified during these 3 weeks. Baseline and post-HD measurements of arterial haemodynamic and biochemical parameters were obtained just prior to the beginning and after termination of experimental HD. The study protocol was approved by the ethics committee of the institution and written consent was obtained from all study participants.

Patients were included if they were 18 years or older, were on chronic HD for more than 3 months with stable dry weight and BP, stable doses of antihypertensive medications and phosphate binders and without any changes in dialysis prescription over the preceding month. Patients were excluded if they had any clinical conditions that would hamper pre- or post-dialysis haemodynamic measurements such as arterial fibrillation, multiple intradialytic hypertensive episodes, severe vascular disease or interdialytic weight gain of >5% of total body weight. Patients with a history of parathyroidectomy or PTH levels of >800 ng/L were also excluded. Twenty-one chronic HD patients were enrolled. Three were excluded because of hypertension (\( n = 1 \)), need to change blood pressure (BP) medication (\( n = 1 \)) and withdrawal of consent (\( n = 1 \)). Eighteen patients completed the study. HD was performed 3-times weekly with a filter of 2.1 m² surface area, a dialysis duration of 3–4 h per session and a blood flow of 350–400 mL/min. A bicomponent-based buffer dialysis solution was used with sodium concentrations of 138–142 mmol/L, potassium concentrations of 1–4 mmol/L and a dialysate flow rate of 500–750 mL/min. The causes of \( \Delta c_{-a} \) were glomerulonephritis (\( n = 4 \)), diabetic nephropathy (\( n = 2 \)), obstructive nephropathy (\( n = 4 \)), interstitial nephritis (\( n = 4 \)), hypertensive nephropathic obstructive glomerulosclerosis (\( n = 2 \)) and unknown (\( n = 2 \)). Patients suffered from hypertension (\( n = 14 \)), atherosclerotic coronary disease (\( n = 4 \)) and peripheral atherosclerotic vascular disease (\( n = 1 \)). One had had a stroke and three had type 2 diabetes. The patients used ACE inhibitors (\( n = 5 \)), calcium-channel blockers (\( n = 10 \)), AT1 receptor blockers (\( n = 5 \)), \( \beta \)-blockers (\( n = 6 \)), central antihypertensive agents (\( n = 3 \)), antiarrhythmics (\( n = 1 \)) and \( \alpha \)-receptor antagonist (\( n = 1 \)). Eight patients took a mean of 6.25 tablets of sevelamer HCl (800 mg) daily, and 15 patients took a mean of 2.5 tablets of oral calcium carbonate (500 mg) daily.

Haemodynamic measurements
The patient was positioned in the supine position and allowed to rest for 15 min prior to their haemodynamic measurements. Brachial artery BP was recorded using an automatic sphygmomanometer BPM-100 (BP-Tru, Coquitlam, Canada). BP was recorded six times, with a 2-min interval between each measurement, and the average of the last five measurements was used to determine the brachial systolic and diastolic blood pressure (SBP) (DBP) [16].

The radial pulse wave profile (rPWP) was recorded by applanation tonometry using the Sphygmocor system® (AtCor Medical Pty Ltd, Sydney, Australia). The tonometer probe was positioned over the radial artery, and a recording of rPWP was obtained for a 10-s period. The rPWP was recalibrated with the systolic and diastolic brachial BP. Three consecutive recordings were performed. A cPWP was then derived from the rPWP using a generalized transfer function as previously validated [17]. Central SBP, DBP, mean BP (MBP), PP and the time of return of the reflected wave (Tr) were derived. Pressure and time of first peak (P1 and T1) and second
peak (P2 and T2), and central augmented pressure (AP) were obtained. Central augmentation index (AiX) was computed (AP = P2−P1; AiX = (AP/PP) × 100) and corrected for a heart rate of 75 beats/minute. The mean ePWP for the entire group under each pre- and post-HD with varying calcium concentration was then constructed as a method to visually assess the modification of ePWP under each experimental HD. This was performed by computing group mean DBP pressure at the end of systole (ESP), pressure of the first and second pressure peak and their respective timing, Tr and duration of cardiac cycle in pre- and post-HD.

### Results

Eighteen patients with a mean age of 48.9 ± 18 years and a median duration of chronic HD of 8.7 months (range 1–87 months) completed the study. The participants included 5 women and 13 men. Baseline DCa were 1.00 mmol/L (n = 11) and 1.50 mmol/L (n = 6). Pre-HD levels of PTH, iCa, BP, c-f PWV, c-r PWV, AiX and Tr were not significantly different between each experimental HD session. The average ultrafiltration was 2.0 ± 1.0 L, 1.9 ± 1.1 L and 2.1 ± 1.1 L for DCa of 1.00, 1.25 and 1.50 mmol/L, respectively (P = 0.78 for repeated measures ANOVA). There were no significant effects of sequence on the extent of haemodynamic and biochemical parameters. Therefore, the residual effects of the previous DCa of one experimental HD session were considered to be negligible on the subsequent experimental HD.

A two-way analysis of variance for repeated measures was conducted to study the effects of HD, DCa and HD–DCa interaction on biochemical and haemodynamic variables. The results are presented in Tables 1 and 2.
Table 2. Central pulse wave profile parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-HD</th>
<th>Post-HD</th>
<th>Pre-HD Δ</th>
<th>Post-HD Δ</th>
<th>Repeated measures ANOVA</th>
<th>Linear contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ca</td>
<td>HD</td>
</tr>
<tr>
<td>1.00</td>
<td>120 ± 19</td>
<td>115 ± 15</td>
<td>120 ± 18</td>
<td>0.003</td>
<td>0.15</td>
<td>0.006</td>
</tr>
<tr>
<td>1.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.50</td>
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</table>
Table 3. Determinants of variation in arterial stiffness and wave reflection

<table>
<thead>
<tr>
<th></th>
<th>Estimate (95% confidence interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>%Δ c-f PWV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔiCa (mmol/L)</td>
<td>0.566 (0.018–1.114)</td>
<td>0.043</td>
</tr>
<tr>
<td>ΔMBP (mmHg)</td>
<td>0.002 (−0.002–0.006)</td>
<td>0.279</td>
</tr>
<tr>
<td>%Δ c-r PWV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔiCa (mmol/L)</td>
<td>0.654 (0.063–1.247)</td>
<td>0.031</td>
</tr>
<tr>
<td>ΔMBP (mmHg)</td>
<td>0.003 (−0.001–0.007)</td>
<td>0.131</td>
</tr>
<tr>
<td>%Δ Tr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔMBP (mmHg)</td>
<td>−0.001 (−0.002–0.0008)</td>
<td>0.013</td>
</tr>
<tr>
<td>UF (L)</td>
<td>−0.012 (−0.023 to −0.0003)</td>
<td>0.045</td>
</tr>
<tr>
<td>%Δ AIx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔMBP (mmHg)</td>
<td>0.597 (0.382–0.812)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔHR (b.p.m.)</td>
<td>−0.420 (−0.660 to −0.179)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Linear-mixed model for repeated measure. Covariates in the model include ultrafiltration (UF), changes in the heart rate (ΔHR), ionized calcium (AIiCa), mean blood pressure (ΔMBP) and parathyroid hormone levels.

change in AIx was inversely determined by the variation in the heart rate and directly with ΔMBP.

Discussion

In this study, we evaluated acute changes in arterial stiffness and cPWP during 3 HD sessions differing only by the Dca that ranged from 1.00 to 1.50 mmol/L, thereby modulating serum iCa concentrations within the physiological range. Our results show that a rise in serum iCa during one HD session, even within the physiological range of calcaemia, is associated with an increase in PWV of both muscular and elastic type arteries. In addition, higher levels of calcaemia were associated with a lesser decrease in post-HD central BP and a more rapid return of the reflected wave (earlier Tr) without any significant change in AIx. Our findings are in keeping with previous studies comparing the haemodynamic effects of Dca of 1.25 and 1.75 mmol/L. However, in light of growing concern regarding positive calcium balance, the Dca of 1.75 mmol/L is no longer recommended for standard three times weekly dialysis sessions [19]. Therefore, there was a need to evaluate the haemodynamic effects of the presently used DCa.

PWV is an established method of evaluating segmental arterial stiffness and has repeatedly been associated with clinical outcomes, especially in a HD population [20,21]. The acute changes of PWV in our study, however, were transitory and so are believed to be functional changes as it is highly unlikely that they would induce acute structural changes. They are most likely the result of variation in vascular smooth muscle cell (VSMC) tone that is highly dependent on the extracellular calcium concentration. Earlier Tr could be explained by either an increase in PWV and/or proximalization of the reflection sites. However, using a linear-mixed model, we found no significant association between the degree of increase in either c-rPWV or c-f PWV and the degree of earlier wave reflection. Therefore, it seems reasonable to assume that the proximalization of arterial reflection sites is a greater determinant of earlier
wave reflection in this experimental study. The proximalization of arterial reflection sites is also thought to result from enhanced vascular tone, which leads to a greater reduction in the lumen of the branching arteries. The fact that an earlier return of the wave reflection is positively associated with the degree of ultrafiltration during the HD session is in keeping with this hypothesis. In this study, Aix seems to be more influenced by variation in heart rate and MBP than by the change in calcemia. In fact, Aix is known to be influenced by factors such as reflection sites, reflection coefficient and heart rate, therefore limiting its utility as a reliable marker of arterial stiffness [22,23].

Marchais et al. [24] have previously shown an increase in both aortic and brancial PWVs with a DCa of 1.75 mmol/L, but not with a DCa of 1.5 mmol/L. In addition, Kyriazis et al. [25] found an increase in stiffness index after one HD with DCa of 1.75 mmol/L as evaluated by digital pulse volume, and Yoo et al. [26] observed an increase in carotid compliance after switching from DCa of 1.75 to a DCa of 1.25 mmol/L for eight consecutive HD sessions. After switching form a DCa of 1.75 to 1.25 mmol/L even for only one HD session, some investigators have shown a significant decrease in peripheral BP [27,28]. In contrast, Kyriazis et al. [29] failed to confirm these observations with only one HD session although they observed a reduction in PP and MBP after switching from DCa 1.75 to 1.25 mmol/L for 10 consecutive HD sessions. There is compelling evidence to support that high extracellular calcium concentrations could induce arterial vasoconstriction in humans [30]. However, higher dialysate calcium concentrations have also been shown to increase cardiac contractility, potentially leading to a higher BP and different pulse profile through increased cardiac output [27,28,31]. In the present study, higher DCa was associated with a higher P1 and an earlier T1, suggesting an increase in myocardial contractility within this range of DCa. The only potential influence of cardiac contractility on arterial PWV could be mediated through the degree of change in arterial MBP. However, in multivariate analysis, the degree of change in the iCa concentration was the only significant determinant of relative change in c-r PWV and c-f PWV.

The haemodynamic changes that were observed in our study may not be solely attributed to the direct effects of iCa on the cardiovascular system. Since iCa has an acute effect on PTH concentrations, it may be possible that at least some of the effect could be mediated through the actions of PTH. Indeed, based on animal experiments, it has been suggested that acute PTH administration can result in the reduction of BP [32]. In this regard, PTH may act directly as a vasorelaxant on VSMC via cAMP-dependent inhibition of L-type Ca++ channel currents [33]. It could be argued that in our study, the suppression of PTH by the acute rise in serum calcium concentration could play a significant role in the rise of BP. However, in multivariate analysis, the change in the PTH level was not significantly related to changes in arterial PWV.

In conclusion, this study showed that DCa and acute changes in the serum iCa concentration, even within physiological range, are associated with detectable changes in arterial stiffness of both elastic (c-f segment) and musculartype arteries (c-r segment), and in the PWP of the aorta. More studies are needed to evaluate the consequences of these repetitive effects on the long-term function and structure of arteries in the uraemic milieu.

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Conflict of interest statement. None declared.

References
A randomized, crossover design study of sevelamer carbonate powder and sevelamer hydrochloride tablets in chronic kidney disease patients on haemodialysis

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Abstract

Background. Sevelamer carbonate is an improved, buffered form of sevelamer hydrochloride developed for the treatment of hyperphosphataemia in CKD patients. Sevelamer carbonate formulated as a powder for oral suspension presents a novel, patient-friendly alternative to tablet phosphate binders. This study compared the safety and efficacy of sevelamer carbonate powder with sevelamer hydrochloride tablets in chronic kidney disease patients on haemodialysis.

Methods. This was a multi-centre, open-label, randomized, crossover design study. Thirty-one haemodialysis patients were randomly assigned to either sevelamer carbonate powder or sevelamer hydrochloride tablets for 4 weeks followed by a crossover to the other regimen for an additional 4 weeks.

Results. The mean serum phosphorus was 1.6 ± 0.5 mmol/L (5.0 ± 1.5 mg/dL) during sevelamer carbonate powder treatment and 1.7 ± 0.4 mmol/L (5.2 ± 1.1 mg/dL) during sevelamer hydrochloride tablet treatment. Sevelamer carbonate powder and sevelamer hydrochloride tablets are equivalent in controlling serum phosphorus; the geometric least square mean ratio was 0.95 (90% CI 0.87–1.03). No statistically significant or clinically meaningful differences were observed in calcium × phosphorus product and lipid

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