16. Schwab S, Oliver M, Suhocki P *et al*. Hemodialysis arteriovenous access: detection of stenosis and response to treatment by vascular access blood flow. *Kidney Int* 2001; 5: 358–362
17. Kian K, Wyatt C, Schon D *et al*. Safety of low-dose radiocontrast for interventional AV fistula salvage in stage 4 chronic kidney disease patients. *Kidney Int* 2006; 69: 1444–1449
18. Le Blanche A, Tassart M, Deux J *et al*. Gadolinium-enhanced digital subtraction angiography of hemodialysis fistulas: a diagnostic and therapeutic approach. *Am J Roentgenol* 2002; 179: 1023–1028
19. Sacks D, Marinelli D, Martin L *et al*. and the members of the technology assessment committee. Reporting standards for clinical evaluation of new peripheral arterial revascularization devices. *J Vasc Interv Radiol* 1997; 8: 137–149
20. Gray R, Sacks D, Martin L *et al*. and the members of the Society of Interventional Radiology technology assessment committee. Reporting standards for percutaneous interventions in dialysis access. *J Vasc Interv Radiol* 2003; 10: 1405–1415
21. Turmel-Rodrigues L, Raynaud A, Louail B *et al*. Manual catheter-directed aspiration and other thrombectomy techniques for declotting native fistulas for hemodialysis. *J Vasc Interv Radiol* 2001; 12: 1365–1371
22. Duncan H, Ferguson L, Faris I. Incidence of the radial steal syndrome in patients with Brescia fistula for hemodialysis: its clinical significance. *J Vasc Surg* 1986; 4: 144–147
23. Malovrh M. Non-invasive evaluation of vessels by duplex sonography prior to construction of arteriovenous fistulas for haemodialysis. *Nephrol Dial Transplant* 1998; 13: 125–129
24. Tordoir J, Rooyens P, Dammers R *et al*. Prospective evaluation of failure modes in autogenous radiocephalic wrist access for haemodialysis. *Nephrol Dial Transplant* 2003; 18: 378–383
25. Bourquelot P. Preventive haemostasis with an inflatable tourniquet for microsurgical distal arteriovenous fistulas for haemodialysis. *Microsurgery* 1993; 14: 462–463
26. Keuter X, Kessels A, de Haan M *et al*. Prospective evaluation of ischemia in brachial-basilic and forearm prosthetic arteriovenous fistulas for hemodialysis. *Eur J Vasc Endovasc Surg* 2008; 35: 619–624
27. Könner K, Hulbert-Shearon T, Roys E *et al*. Tailoring the initial vascular access for dialysis patients. *Kidney Int* 2002; 62: 329–338
28. Tynan-Cuisinier G, Berman S. Strategies for predicting and treating access-induced ischemic steal syndrome. *Eur J Vasc Endovasc Surg* 2006; 32: 309–315
29. Zanow J, Kurger U, Scholz H. Proximalization of the arterial inflow: a new technique to treat access-related ischemia. *J Vasc Surg* 2006; 43: 1216–1221
30. Basile C, Lomonte C, Vernaglione L *et al*. The relationship between the flow of arteriovenous fistula and cardiac output in haemodialysis patients. *Nephrol Dial Transplant* 2008; 23: 282–287
31. Guerra A, Raynaud A, Beyssen B *et al*. Arterial percutaneous angioplasty in upper limbs with vascular access devices for haemodialysis. *Nephrol Dial Transplant* 2002; 17: 843–848

Received for publication: 23.3.09; Accepted in revised form: 11.6.09

Nephrol Dial Transplant (2009) 24: 3788–3794
doi: 10.1093/ndt/gfp351
Advance Access publication 4 August 2009

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

Amélie LeBeouf[1], Fabrice Mac-Way[1], Mihai Silviu Utescu[1], Nadia Chbinou[1], Pierre Douville[2], Simon Desmeules[1] and Mohsen Agharazii[1]

[1]Division of Nephrology and [2]Division of Medical Biochemistry, Research Center of CHUQ, L'Hôtel Dieu de Québec Hospital and Faculty of Medicine, Laval University, Quebec, QC, Canada

Correspondence and offprint requests to: Mohsen Agharazii; E-mail: mohsen.agharazii@crhdq.ulaval.ca

Abstract

Background. Abnormal mineral metabolism in chronic kidney disease plays a critical role in vascular calcification and arterial stiffness. The impact of presently used dialysis 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 D_{Ca} of 1.25 mmol/L. Tests of within-subject contrast showed a linear relationship between higher D_{Ca} and a higher post-HD Δc-f PWV, Δc-r PWV and Δmean BP ($P < 0.001$, $P = 0.008$ and $P = 0.002$, respectively). Heart rate-adjusted central augmentation index (AIx) decreased significantly after HD, but was not related to D_{Ca}. The timing of wave refection (Tr) occurred earlier after dialysis resulting in a linear relationship between higher D_{Ca} 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 ΔMBP was not significant. In contrast, the percentage decrease in Tr (earlier wave reflection) was determined by higher ΔMBP and higher ultrafiltration, whereas the relative change in AIx was inversely determined by the variation in the heart rate and directly by ΔMBP.

Conclusion. We conclude that D_{ca} 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 D_{Ca} 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 carotido-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 (D_{Ca}) in the overall calcium balance. Although, DOQI guidelines recommend a D_{Ca} of 1.25 mmol/L, the optimal D_{Ca} 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 calcaemia, 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 D_{Ca} 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 D_{Ca} for 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. Each subject was randomly assigned to one of the three different sequences of D_{Ca}: sequence 1 (D_{Ca} of 1.00, 1.25, 1.50 mmol/L), sequence 2 (D_{Ca} of 1.25, 1.50 and 1.00 mmol/L) and sequence 3 (D_{Ca} 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 hypotensive 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 hypotension ($n = 1$), 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 m^2 surface area, a dialysis duration of 3–4 h per session and a blood flow of 350–400 mL/min. A bicarbonate-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 CKD were glomerulonephritis ($n = 4$), diabetic nephropathy ($n = 2$), obstructive nephropathy ($n = 4$), interstitial nephritis ($n = 4$), hypertensive nephroangiosclerosis ($n = 2$) 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 ($n = 5$), β-blockers ($n = 6$), central antihypertensive agents ($n = 3$), antiarrhythmics ($n = 1$) and α_1-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

Table 1. Biochemical and haemodynamic parameters

	D_{Ca} (mmol/L)			Repeated measures ANOVA			Linear contrast
	1.00	1.25	Ca × HD	Ca	HD	HD × Ca	HD × Ca
iCa (mmol/L)							
Pre-HD	1.17 ± 0.05	1.16 ± 0.05	1.17 ± 0.06	<0.001	0.09	<0.001	<0.001
Post-HD Δ	−0.14 ± 0.04	−0.02 ± 0.05	0.10 ± 0.06				
PTH							
Pre-HD	223 ± 170	220 ± 150	199 ± 145	<0.001	0.68	<0.001	<0.001
Post-HD Δ	237 ± 196	49 ± 205	−104 ± 103				
Brachial SBP (mmHg)							
Pre-HD	129 ± 18	125 ± 16	130 ± 19	0.003	0.29	0.001	0.001
Post-HD Δ	−10 ± 19	−5 ± 15	3 ± 14				
Brachial DBP (mmHg)							
Pre-HD	79 ± 9	79 ± 11	79 ± 11	0.03	0.75	0.005	0.014
Post-HD Δ	−2 ± 9	−3 ± 11	4 ± 8				
Heart rate (b.p.m.)							
Pre-HD	70 ± 12	70 ± 17	69 ± 10	0.20	0.74	0.46	0.28
Post-HD Δ	2 ± 13	0.4 ± 8	−0.7 ± 7				
c-f PWV (m/s)							
Pre-HD	11.6 ± 3.1	11 ± 1.8	11 ± 2.7	0.84	0.17	0.001	<0.001
Post-HD Δ	−0.8 ± 1.4	0.9 ± 1.9	0.8 ± 0.9				
c-r PWV (m/s)							
Pre-HD	10.3 ± 1.9	9.8 ± 1.6	9.8 ± 1.7	0.87	0.003	0.028	0.008
Post-HD Δ	0.16 ± 1.3	0.99 ± 1.4	1.2 ± 1.4				

D_{Ca}, dialysate calcium concentration; iCa, ionized calcium; PTH, parathyroid hormone; SBP, systolic blood pressure; DBP, diastolic blood pressure; c-f PWV, carotido-femoral pulse wave velocity; c-r PWV, carotido-radial pulse wave velocity.

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 cPWP 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 cPWP 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.

Assessment of PWV was made using Complior® SP (Artech Medical, Pantin, France). We first recorded the carotido-radial (c-r) PWV by positioning one sensor over the radial artery and a second sensor over the carotid artery. The distance between the two sensors was measured with a measuring tape, and three consecutive recordings of both pulse waveforms were performed (8–10 heart beats for each recording). The Complior software automatically detected the foot of each pulse waveform from the two arterial sites and then measured the mean distance between the two feet as being the travel time of the wave. PWV was then computed using the following formula: PWV = travel distance/travel time, as previously validated [18]. C-f PWV was also determined using the same technique but positioning the second sensor on the femoral artery.

Biochemical measurements

Blood samples were obtained immediately before the start of each experimental HD session and at the end of each of these sessions. Ionized calcium (iCa), intact parathyroid hormone (PTH) and albumin were monitored. iCa was measured with an ion-selective electrode on a Nova PhoxPlus analyser. Intact PTH (1–84) was measured with the PTH stat assay from Roche diagnostics using two antibodies reactive with epitopes in the amino acid regions 26–32 and 37–42.

Data analysis

Data analysis was performed using the SPSS software (version 16.0 for Windows, SPSS Inc., Chicago, IL, USA). Data were expressed as means ± SD. To study the effect of HD, D_{Ca} and HD–D_{Ca} interaction on biochemical and haemodynamic variables, we used general linear model two-way analysis of variance for repeated measures. Sphericity was verified by Mauchly's test of sphericity, and in the case of sphericity deviation, the *P*-value was corrected according to the Greenhouse–Geisser epsilon coefficient for probability adjustment. This procedure was followed by a polynomial within-subject linear contrast to study the linearity between D_{Ca} and post-HD variation of biochemical and haemodynamic parameters. A general linear mixed model showed no significant sequence or carryover effects on haemodynamic parameters. To account for repeated observations, the general linear-mixed model was used to study the determinants of relative changes of c-f PWV, c-r PWV, AIx and Tr by entering ultrafiltration, Δheart rate, ΔMBP and ΔiCa and log of PTH ratio as covariates. Bonferroni correction was used for multiple comparisons between treatment groups when appropriate. A *P*-value of <0.05 was considered to be statistically significant.

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 D_{Ca} were 1.00 mmol/L (n = 1), 1.25 mmol/L (n = 11) and 1.50 mmol/L (n = 6). Pre-HD levels of PTH, iCa, BP, c-r PWV, c-f 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 D_{Ca} 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 D_{Ca} 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, D_{Ca} and HD–D_{Ca} interaction on biochemical and haemodynamic variable. The results are presented in Tables 1 and 2.

Table 2. Central pulse wave profile parameters

	D_{Ca} (mmol/L)			Repeated measures ANOVA			Linear contrast
	1.00	1.25	1.50	Ca	HD	Ca × HD	Ca × HD
SBP (mmHg)							
Pre-HD	120 ± 19	115 ± 15	120 ± 18	0.003	0.15	0.006	0.001
Post-HD Δ	−10 ± 21	−7 ± 16	0.8 ± 15				
DBP (mmHg)							
Pre-HD	80 ± 10	80 ± 11	80 ± 11	0.024	0.71	0.007	0.018
Post-HD Δ	−2 ± 9	−3 ± 11	3 ± 8				
MBP (mmHg)							
Pre-HD	97 ± 12	95 ± 12	97 ± 12	0.003	0.229	0.001	0.002
Post-HD Δ	−6 ± 11	−5 ± 13	2 ± 10				
ESP (mmHg)							
Pre-HD	108 ± 16	105 ± 14	109 ± 16	0.002	0.59	0.001	0.001
Post-HD Δ	−6 ± 17	−4 ± 15	5 ± 13				
ED (ms)							
Pre-HD	320 ± 20	317 ± 17	320 ± 19	0.75	<0.001	0.98	0.97
Post-HD Δ	−49 ± 37	−48 ± 31	−49 ± 27				
AIx (%)							
Pre-HD	22 ± 10	22 ± 9	22 ± 9	0.51	0.004	0.73	0.97
Post-HD Δ	−8 ± 14	−9 ± 11	−8 ± 11				
Tr (ms)							
Pre-HD	143 ± 11	145 ± 13	144 ± 12	0.10	<0.001	0.093	0.044
Post-HD Δ	−4 ± 8	−6 ± 5	−9 ± 6				

Pre-HD, pre-haemodialysis value; post-HDΔ, absolute post-dialysis variation of each parameter; D_{Ca}, dialysate calcium concentration; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; ESP, end systolic pressure; ED, ejection duration; AIx, heart augmentation index; Tr, time to the start of the reflected wave.

Biochemical parameters

HD *per se* had no significant effect on the levels of iCa and PTH. D_{Ca} and HD–D_{Ca} interaction were statistically significant for iCa and PTH (Table 1).

Arterial stiffness

HD was associated with the post-HD increase in c-r PWV ($P = 0.003$). D_{Ca} had a significant effect on systolic and diastolic BP ($P = 0.003$ and $P = 0.03$, respectively). There was a significant relationship between D_{Ca} and post-HD Δc-f PWV and Δc-r PWV ($P = 0.001$ and $P = 0.028$ for HD–D_{Ca} interaction). In addition, the tests of within-subject contrast showed a linear effect of D_{Ca} on post-HD Δc-f PWV and Δc-r PWV ($P < 0.001$ and $P = 0.008$, respectively).

Central pulse wave profile

Table 2 shows the effects of HD, D_{Ca} and HD–D_{Ca} interaction on central haemodynamic parameters as derived from cPWP. HD was associated with the post-HD reduction in heart rate adjusted AIx ($P = 0.004$), ejection duration ($P < 0.001$) and Tr ($P < 0.001$). D_{Ca} had a significant effect on central SBP ($P = 0.003$), DBP ($P = 0.024$), MBP ($P = 0.003$) and ESP ($P = 0.002$). The HD–D_{Ca} interaction was statistically significant for central SBP ($P = 0.006$), DBP ($P = 0.007$), MBP ($P = 0.001$) and ESP ($P = 0.001$).

A representative example of a cPWP from a middle-age patient suffering from CKD, as derived from the radial PWP, is presented in Figure 1. Using the average BP at various time points of cPWP, we constructed a pre- and post-HD mean cPWP for the sample population under each experimental HD (Figure 2). The use of D_{Ca} of 1.25 mmol/L did not affect any of the pressures. The tests of within-subject linear contrast showed a statistically significant effect of D_{Ca} on post-HD ΔDBP, ΔP1, ΔP2, ΔESP, Δmean pressure of diastole, ΔT1 and ΔTr ($P < 0.05$). However, no relationship was observed between D_{Ca} and post-HD changes in T2, ejection duration and heart rate.

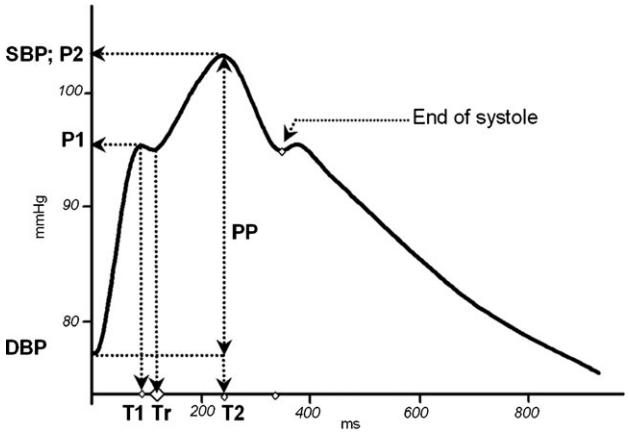

Fig. 1. Central pulse wave profile. The central pulse wave profile can be broken into the following parameters: first peak of pressure (P1), second peak of pressure (P2), time at P1 (T1), time at P2 (T2), time of return of the reflection wave (Tr), diastolic blood pressure (DBP), systolic blood pressure (SBP), pulse pressure (PP).

Determinants of haemodynamic variation

In a multivariate linear-mixed model for repeated measures, the percentage increase in c-f PWV and c-r PWV was

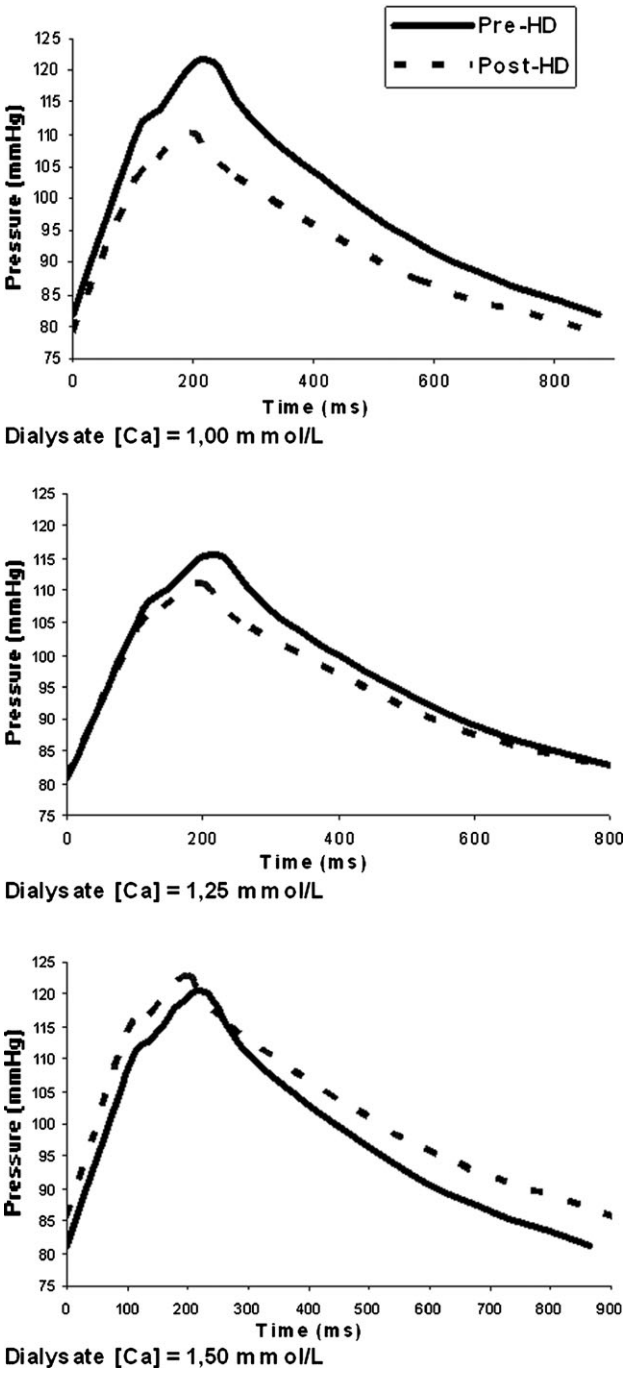

Fig. 2. Mean pre- and post-haemodialysis central pressure waveform. Using the mean pressure points at corresponding time points of each patient ($n = 18$), the group's central pulse wave profile (cPWP) was constructed for each treatment group. The solid line and dotted lines indicate the pre- and post-HD cPWP, respectively. The top, middle and lower panels, respectively, refer to dialysate calcium concentrations of 1.00, 1.25 and 1.50 mmol/L.

significantly associated with the increasing level of iCa, whereas the changes in the level of MBP were not significant (Table 3). However, the percentage decrease in Tr (earlier wave reflection) was determined mainly by higher ΔMBP and higher degree of ultrafiltration. The relative change in AIx was inversely determined by the variation in the heart rate and directly with ΔMBP.

Table 3. Determinants of variation in arterial stiffness and wave reflection

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

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

Discussion

In this study, we evaluated acute changes in arterial stiffness and cPWP during 3 HD sessions differing only by the D_{ca} 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 D_{ca} of 1.25 and 1.75 mmol/L. However, in light of growing concern regarding positive calcium balance, the D_{ca} 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 D_{Ca}.

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 calcaemia. 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 D_{Ca} of 1.75 mmol/L, but not with a D_{Ca} of 1.5 mmol/L. In addition, Kyriazis *et al*. [25] found an increase in stiffness index after one HD with D_{ca} 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 D_{ca} of 1.75 to a D_{ca} of 1.25 mmol/L for eight consecutive HD sessions. After switching form a D_{Ca} of 1.75 to 1.25 mmol/L even for only one HD session, some investigators have shown a significant decrease in peripherial 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 D_{ca} 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 D_{Ca} was associated with a higher P1 and an earlier T1, suggesting an increase in myocardial contractility within this range of D_{Ca}. 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 D_{ca} 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 muscular-type 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.

Acknowledgements. This project was supported by the Canadian Institute of Health Research, New Emerging Team Grant (NET-54008), the Heart & Stroke Foundation of Canada, the Kidney Foundation of Canada and the Canadian Diabetes Association. M.A. holds a scholarship from Fonds de Recherche en Santé du Québec and A.L. holds a scholarship from the Canadian Institutes of Health Research and Le Fonds de la Recherche en Santé du Québec.

Conflict of interest statement. None declared.

References

1. Blacher J, Guerin AP, Pannier B *et al*. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 1999; 99: 2434–2439
2. Blacher J, Safar ME, Guerin AP *et al*. Aortic pulse wave velocity index and mortality in end-stage renal disease. *Kidney Int* 2003; 63: 1852–1860
3. London GM, Marchais SJ, Guerin AP *et al*. Cardiac hypertrophy and arterial alterations in end-stage renal disease: hemodynamic factors. *Kidney Int Suppl* 1993; 41: S42–S49
4. Marchais SJ, Guerin AP, Pannier BM *et al*. Wave reflections and cardiac hypertrophy in chronic uremia. Influence of body size. *Hypertension* 1993; 22: 876–883
5. London GM. The concept of ventricular/vascular coupling: functional and structural alterations of the heart and arterial vessels go in parallel. *Nephrol Dial Transplant* 1998; 13: 250–253
6. London GM. Alterations of arterial function in end-stage renal disease. *Nephron* 2000; 84: 111–118
7. London GM, Pannier B, Guerin AP *et al*. Alterations of left ventricular hypertrophy in and survival of patients receiving hemodialysis: follow-up of an interventional study. *J Am Soc Nephrol* 2001; 12: 2759–2767
8. Haydar AA, Covic A, Colhoun H *et al*. Coronary artery calcification and aortic pulse wave velocity in chronic kidney disease patients. *Kidney Int* 2004; 65: 1790–1794
9. Blacher J, Guerin AP, Pannier B *et al*. Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. *Hypertension* 2001; 38: 938–942
10. Bruel A, Oxlund H. Changes in biomechanical properties, composition of collagen and elastin, and advanced glycation endproducts of the rat aorta in relation to age. *Atherosclerosis* 1996; 127: 155–165
11. Winlove CP, Parker KH, Avery NC *et al*. Interactions of elastin and aorta with sugars *in vitro* and their effects on biochemical and physical properties. *Diabetologia* 1996; 39: 1131–1139
12. Goodman WG, Goldin J, Kuizon BD *et al*. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000; 342: 1478–1483
13. McIntyre CW. Calcium balance during hemodialysis. *Semin Dial* 2008; 21: 38–42
14. Essalihi R, Zandvliet ML, Moreau S *et al*. Distinct effects of amlodipine treatment on vascular elastocalcinosis and stiffness in a rat model of isolated systolic hypertension. *J Hypertens* 2007; 25: 1879–1886
15. Raggi P, Bellasi A, Ferramosca E *et al*. Association of pulse wave velocity with vascular and valvular calcification in hemodialysis patients. *Kidney Int* 2007; 71: 802–807
16. Mattu GS, Perry TL Jr, Wright JM. Comparison of the oscillometric blood pressure monitor (BPM-100(Beta)) with the auscultatory mercury sphygmomanometer. *Blood Press Monit* 2001; 6: 153–159
17. Chen CH, Nevo E, Fetics B *et al*. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. *Circulation* 1997; 95: 1827–1836
18. Asmar R, Benetos A, Topouchian J *et al*. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. *Hypertension* 1995; 26: 485–490

19. K/DOQI. Clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003; 42: S1–S201
20. Laurent S, Boutouyrie P, Asmar R *et al*. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; 37: 1236–1241
21. Blacher J, Asmar R, Djane S *et al*. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. *Hypertension* 1999; 33: 1111–1117
22. Vyas M, Izzo JL Jr, Lacourciere Y *et al*. Augmentation index and central aortic stiffness in middle-aged to elderly individuals. *Am J Hypertens* 2007; 20: 642–647
23. Woodman RJ, Kingwell BA, Beilin LJ *et al*. Assessment of central and peripheral arterial stiffness: studies indicating the need to use a combination of techniques. *Am J Hypertens* 2005; 18: 249–260
24. Marchais S, Guerin A, Safar M *et al*. Arterial compliance in uraemia. *J Hypertens Suppl* 1989; 7: S84–S85
25. Kyriazis J, Katsipi I, Stylianou K *et al*. Arterial stiffness alterations during hemodialysis: the role of dialysate calcium. *Nephron Clin Pract* 2007; 106: c34–c42
26. Yoo SJ, Oh DJ, Yu SH. The effects of low calcium dialysate on arterial compliance and vasoactive substances in patients with hemodialysis. *Korean J Intern Med* 2004; 19: 27–32
27. Van Der Sande FM, Cheriex EC, van Kuijk WH *et al*. Effect of dialysate calcium concentrations on intradialytic blood pressure course in cardiac-compromised patients. *Am J Kidney Dis* 1998; 32: 125–131
28. van Kuijk WH, Mulder AW, Peels CH *et al*. Influence of changes in ionized calcium on cardiovascular reactivity during hemodialysis. *Clin Nephrol* 1997; 47: 190–196
29. Kyriazis J, Stamatiadis D, Mamouna A. Intradialytic and interdialytic effects of treatment with 1.25 and 1. 75 mmol/L of calcium dialysate on arterial compliance in patients on hemodialysis. *Am J Kidney Dis* 2000; 35: 1096–1103
30. Scholze A, Maier A, Stocks F *et al*. Sustained increase of extracellular calcium concentration causes arterial vasoconstriction in humans. *J Hypertens* 2005; 23: 2049–2054
31. Henrich WL, Hunt JM, Nixon JV. Increased ionized calcium and left ventricular contractility during hemodialysis. *N Engl J Med* 1984; 310: 19–23
32. Pang PK, Tenner TE Jr, Yee JA *et al*. Hypotensive action of parathyroid hormone preparations on rats and dogs. *Proc Natl Acad Sci USA* 1980; 77: 675–678
33. Wang R, Wu LY, Karpinski E *et al*. The effects of parathyroid hormone on L-type voltage-dependent calcium channel currents in vascular smooth muscle cells and ventricular myocytes are mediated by a cyclic AMP dependent mechanism. *FEBS Lett* 1991; 282: 331–334

Received for publication: 17.3.09; Accepted in revised form: 25.6.09

Nephrol Dial Transplant (2009) 24: 3794–3799
doi: 10.1093/ndt/gfp372
Advance Access publication 7 August 2009

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

Stanley Fan[1], Calum Ross[2], Sandip Mitra[3], Philip Kalra[4], Jeremy Heaton[5], John Hunter[5], Melissa Plone[5] and Nick Pritchard[6]

[1]Department of Nephrology, Royal London Hospital, London, [2]Department of Nephrology, Norfolk and Norwich University Hospital, Norwich, [3]Department of Nephrology, Manchester Royal Infirmary, Manchester, [4]Department of Nephrology, Salford Royal Hospital, Salford, UK, [5]Clinical Research Department, Genzyme Corporation, Cambridge, MA, USA and [6]Department of Nephrology, Addenbrooke's Hospital, Cambridge, UK

Correspondence and offprint requests to: Stanley Fan; E-mail: s.fan@qmul.ac.uk

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 CKD 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