Original Paper

Blood Purification

Blood Purif 2004;22:469–472
DOI: 10.1159/000081694

Accepted: July 27, 2004
Published online: October 27, 2004

Increase in Serum Ionized Calcium during Diffusive Dialysis Does Not Affect Left Ventricular Diastolic Function

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Key Words
Left ventricular diastolic function · Echocardiography · Preload dependence · Diffusive dialysis · Serum ionized calcium

Abstract
An increase in serum Ca^{2+} during hemodialysis (HD) may lead to impaired left ventricular (LV) relaxation. Since LV diastolic function assessment in dialysis patients is hampered by preload dependence of Doppler measurements, we tested the effect of HD without ultrafiltration (UF) on these measurements. Transmitral E and A velocities, and mitral annulus *e* and *a* velocities were measured in 10 patients before and after 1 h of HD without UF. Dialysate Ca^{2+} was 1.75 mmol/l. Serum Ca^{2+} after 1 h (1.31 mmol/l; 1.28–1.46 mmol/l) was higher (p = 0.002) than before HD (1.24 mmol/l; 1.09–1.32 mmol/l). E/A (0.8; 0.4–2.8) and *e/a* (0.7; 0.4–1.3) after 1 h were not different than E/A (0.8; 0.6–5.1) and *e/a* (0.7; 0.4–1.8) before HD. The increase in serum Ca^{2+} does not lead to a change in Doppler parameters of LV diastolic function. Changes in these parameters after combined HD-UF are related to preload, not to serum Ca^{2+}.

Introduction

Left ventricular (LV) diastolic dysfunction is considered to be an important factor in the pathogenesis of intradialytic hypotension. An increase in serum ionized calcium concentration in the course of the hemodialysis (HD) procedure could lead to impaired cardiac relaxation. A dialysate solution with a calcium concentration of 1.75 mmol/l is frequently used to prevent a negative calcium balance, especially in dialysis patients using phosphate binders that do not contain calcium. The resulting increase in serum ionized calcium may account for the changes in Doppler parameters of LV diastolic function we observed during echocardiography shortly after HD [1]. However, the diagnosis of LV diastolic dysfunction is not easy to establish in the HD population. Accurate echocardiographic assessment of LV diastolic function in dialysis patients is hampered by the preload dependence of conventional Doppler transmitral flow measurements [2, 3]. A new Doppler technique, mitral annulus velocity by Doppler Tissue Imaging (DTI), has been proposed as a relatively preload-independent parameter of LV diastolic function [4–6]. However, we recently showed this Doppler parameter to display a similar pattern of preload dependence [1]. Volume status is therefore a confounding factor in dialysis patients, in whom filling pressures change independent of a change in cardiac function, as the volume status is directly altered by ultrafiltration (UF). Predialysis overhydration leads to a high preload, which may mask impairment of early diastolic filling. Conversely, HD with UF reduces preload, resulting in decreased peak early filling velocities and a pattern of diastolic dysfunction. So it is clear that in the assessment of LV diastolic function in dialysis patients, the effect of preload changes is crucial and must be accounted for. We therefore focussed on the effect of dialy-

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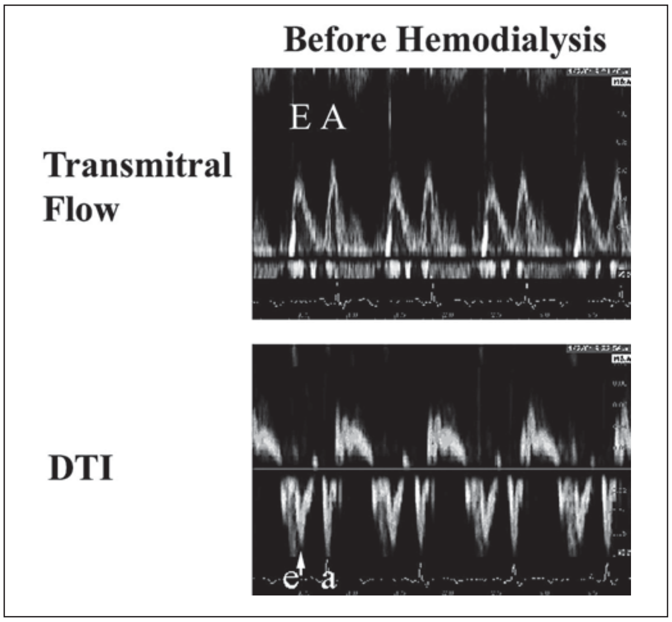

Fig. 1. Peak early (E) and atrial (A) transmitral pulsed-wave Doppler velocities. Using Doppler tissue imaging (DTI), two distinct signals that are directed away from the LV centroid, are obtained during early (e) and late (a) diastole.

sis-induced calcium changes on LV diastolic function in the absence of volume status alteration. In the present study, we tested the effect of isolated diffusive HD without UF on transmitral flow measurements and mitral annulus velocity by DTI.

Methods

Patients

Ten HD patients (8 men and 2 women, median age 60 years, range 37–77 years) were included in this study. Median time on HD was 11 months (range 2 to 59 months). One patient had undergone coronary artery bypass graft surgery 13 years before, and percutaneous transluminal coronary angioplasty (PTCA) with stent placement 3 years before. One patient had a history of unstable angina pectoris treated successfully by PTCA with stent placement 2 years before. Eight patients had no history of cardiac disease. None of the patients had symptomatic ischemic heart disease, significant (>1+) valvular disease or congestive heart failure.

Hemodialysis

All patients were dialyzed following a standard dialysis prescription, which had remained unchanged for several weeks. Dry weight was considered optimal when patients remained without symptoms of dyspnea, orthopnea or edema during the interdialytic period.

All dialysis treatments used a Fresenius 4008 H machine, biocompatible membranes (Hemophane or Polysulphone) and bicarbonate-buffered dialysate (Fresenius Medical Care SK-F213). Standard dialysate was used in all patients. Composition was as follows: Ca^{2+} 1.75, Na^+ 138, K^+ 2.00, and HCO_3^- 32.00 mmol/l.

Study Design

The duration of the dialysis procedure was 4 h in all patients. During the first hour, no UF took place. Two-dimensional echocardiography and Doppler studies were performed before HD and after 1 h. Thereafter, the dialysis session was continued following their dialysis prescription, which included UF. Serum ionized calcium concentration was measured at before, after 1 h of HD and after 4 h at the end of HD.

Echocardiography

Echocardiograms were obtained using a Hewlett Packard Sonos 5500 machine equipped with a 3.5-MHz transducer (Hewlett Packard, Andover, Mass., USA). The same experienced echocardiographer performed all measurements. LV dimensions were measured from the apical four-chamber or parasternal long-axis view. LV mass is reported as LV mass index (LVMI) by height according to the Framingham Study [7]. Fractional shortening (FS) of the LV short axis was measured to obtain an estimate of LV systolic function. Transmitral pulsed-wave Doppler flow velocities were recorded in the apical four-chamber or apical long-axis view. The sample volume was located at the tips of the mitral valve leaflets. Peak E and A transmitral flow velocities were measured (fig. 1). With the use of DTI, in which the sample volume was located at the interventricular septal wall at the level of the mitral annulus, the velocities of motion of the mitral annulus were recorded in spectral pulsed-mode. Data were recorded on videotape, digitized and transferred to a magneto-optical disk. In an off-line workstation, five consecutive beats were analyzed, and mean velocity values were calculated in order to minimize the measurement variability resulting from respiration.

Statistical Analysis

The changes in echo Doppler parameters before and after 1 h of dialysis were analyzed by the Wilcoxon matched-pairs test. The serial measurements of serum ionized calcium before, after 1 h and at the end of HD were compared using Friedman's ANOVA by ranks. If significant, this was followed by a post hoc test using Dunn's analysis. $p < 0.05$ was considered to indicate statistical significance. Data are presented as median values and range.

Results

The dialysis sessions in all patients were uneventful, and none of the patients complained of cramps. At baseline, before HD was initiated, the serum ionized calcium concentration was within the normal range in all but one of the patients (1.24 mmol/l; 1.09–1.32 mmol/l) (table 1). Serum ionized calcium after 1 h (1.31 mmol/l; 1.28–1.46 mmol/l) was significantly higher ($p = 0.002$). There was a further rise in serum ionized calcium until the end of HD after 4 h (1.38 mmol/l; 1.24–1.48 mmol/l), which was not significant. Hematocrit (0.32; 0.25–0.35) and se-

Table 1. Serum ionized Ca^{2+} concentration (mmol/l) at baseline, after 1 h of HD without UF, and after 4 h of HD, using a dialysate with Ca^{2+} 1.75 mmol/l

Patient	Baseline	After 1 h	After 4 h
1	1.18	1.31	1.28
2	1.15	1.28	1.31
3	1.21	1.31	1.40
4	1.24	1.46	1.48
5	1.23	1.33	1.38
6	1.27	1.29	1.24
7	1.32	1.40	1.45
8	1.27	1.30	1.36
9	1.09	1.29	1.41
10	1.24	1.35	1.37
Median	1.22	1.33[a]	1.37[a, b]

[a] Ca^{2+} after 1 h and Ca^{2+} after 4 h are significantly ($p < 0.05$) different from baseline.
[b] Ca^{2+} after 4 h is not significantly different from Ca^{2+} after 1 h.

Table 2. Serum ionized calcium concentration (Ca^{2+}), fractional shortening (FS) and Doppler parameters before and after 1 h of hemodialysis (HD) without ultrafiltration (UF)

	Baseline		After 1 h HD-UF		p
	median	range	median	range	
Ca^{2+}, mmol/l	1.24	1.09–1.31	1.31	1.28–1.46	0.002
FS,%	36	13–48	35	11–44	NS
E, cm/s	68	41–168	58	33–164	NS
A, cm/s	77	33–125	76	56–135	NS
E/A	0.8	0.6–5.1	0.8	0.4–2.8	NS
e, cm/s	6.5	3.4–9.1	6.5	3.0–7.9	NS
a, cm/s	9.0	3.3–13.8	9.4	3.9–11.8	NS
e/a	0.7	0.4–1.8	0.7	0.4–1.3	NS

rum protein (65 g/l; 59–71 g/l) after 1 h were not different from hematocrit (0.33; 0.27–0.36) and serum protein (69 g/l; 60–71 g/l) at baseline.

LVMI at baseline was 128 g/m (86–210 g/m). LV end-diastolic diameter (EDD) (44 mm; 32–55 mm) and FS (35%; 11–44%) after 1 h HD without UF was not different than EDD (44 mm; 39–58 mm) and FS (36%; 13–48%) before HD. Ejection fraction (EF) after 1 h HD without UF (72%; 30–82%) was not different than at baseline (72%; 34–86%). Transmitral E/A after 1 h HD without UF (0.8; 0.4–2.8) was not different than before HD (0.8; 0.6–5.1). Likewise, tissue *e/a* after 1 h HD without UF (0.7; 0.4–1.3) was not different than before HD (0.7; 0.4–1.8) (table 2).

Discussion

In all patients, a 1-hour dialysis session, with a 1.75-mmol/l dialysate calcium concentration, resulted in a significant increase in the serum ionized calcium concentration. This had no effect on transmitral Doppler flow velocities or mitral annulus velocity by DTI. The results of this study show that echo Doppler parameters of LV diastolic function do not change during dialysis without UF, despite a marked increase in serum ionized calcium concentration.

Few studies testing the effect of changes in serum ionized calcium concentration on cardiac function in HD patients have been done. SV measured as a parameter of LV systolic function was found to decrease after HD. This decrease was smaller with a higher dialysate calcium concentration [8, 9]. In these studies, UF was a confounding factor. In our study, visual assessment of LV wall motion before and after HD without UF did not reveal a marked change in contraction pattern. This was confirmed by measuring FS from these two-dimensional images, which did not change. Measurement of LV ejection fraction (EF) is widely used and generally accepted as a parameter of LV systolic function [10]. Median EF in this group was normal and did not change after HD without UF. From these results, it appears that LV contraction is not directly affected by a significant increase in serum ionized calcium.

Only two studies focused on the effect on LV diastolic function. In one of these [11], calcium gluconate was infused at a constant rate of 45 μmol/kg/h to 14 patients with moderate to severe chronic renal failure and secondary hyperparathyroidism. There were no HD patients included in this study. The study population had LV diastolic indices which were not different from a healthy control group and baseline E/A was 1.552, considerably higher than expected in a dialysis population. There was a minor decrease in E/A from 1.552 to 1.414 after calcium infusion. With the use of Student's t test, the authors found this decrease to be significant ($p = 0.03$), although a non-parametric approach might have been more appropriate in view of the small number of patients included. The authors aimed at reaching supranormal levels of serum ionized calcium concentration. The infusion resulted in an increase in mean serum ionized calcium from

1.18 to 1.40 mmol/l. Regarding both the study population and the infusion of calcium to supranormal levels, the experimental conditions of this study clearly do not reflect the setting of a regular dialysis session, such as in our study. We measured the serum calcium concentration at the end of the HD procedure after 4 h, and observed a modest nonsignificant further increase in serum ionized calcium in most, but not all, patients. This indicates that the diffusion of calcium ions is greatest in the first hour of dialysis.

In another study by the same group [12], transmitral flow velocity measurements were made in 12 HD patients before and after three HD sessions with dialysate calcium concentrations of 1.25, 1.50 and 1.75 mmol/l. Serum ionized calcium increased significantly in the 1.50 and 1.75 sessions. Unfortunately, during all sessions, volume was also withdrawn, thereby introducing a confounding factor in this study. Mean total UF varied from 2,120 to 2,580 ml. In view of the well-known phenomenon of preload dependence of transmitral flow velocity measurements, the E/A ratio could be expected to be lower after HD. Indeed, this was the case in all sessions, and it was due to a decrease in peak early velocity (E). However, there was a wide standard deviation, and the differences were not significant, except after the 1.75 mmol/l session.

The utility of transmitral flow velocity measurement as a Doppler parameter of LV diastolic function in HD patients is limited by its preload dependence. In our study, the effect of changes in volume status was precluded, as there was no UF during the first hour. The absence of changes in hematocrit and serum protein indicates that volume shifts resulting from a dialysate-plasma sodium gradient were negligible. We also included mitral annulus velocity measurements by DTI. Although we recently demonstrated this technique to be preload-dependent as well, a change in mitral annulus velocity by DTI, in the absence of UF, may only reflect changes in myocardial tissue relaxation. This could be caused by the shift in serum ionized calcium during diffusive HD. However, as there was no change in *e*, *a* or *e/a*, this newer Doppler parameter of LV diastolic function follows the same pattern as the conventional pulsed-wave Doppler flow velocity measurements. This finding contradicts the view that an increase in serum ionized calcium concentration during a standard dialysis session would lead to impaired LV relaxation.

We conclude that the increase in serum ionized calcium concentration, resulting from diffusive dialysis with a dialysate calcium concentration of 1.75 mmol/l, does not lead to a change in pulsed-wave Doppler transmitral flow velocity or mitral annulus velocity by DTI. These results confirm our hypothesis that changes in Doppler echocardiography parameters of LV diastolic function after a standard HD procedure with UF are related to preload, and not to the increase in serum ionized calcium concentration.

Acknowledgements

This work was presented in part at the American Society of Nephrology, San Diego, Calif., USA, November 2003. The authors gratefully acknowledge Jan Tuin for graphical assistance.

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