The influence of low calcium dialysate on left ventricular diastolic function in peritoneal dialysis patients

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\textbf{ABSTRACT}

Left ventricular (LV) diastolic function was found to be a significant predictor of cardiovascular events and general mortality in dialysis. Studies have indicated that dialysate calcium concentrations were significantly associated with cardiac function. However, the relationship between low calcium dialysate and LV diastolic function has not been clear. The aim of this study was to investigate the influence of low calcium dialysate on cardiac function in peritoneal dialysis (PD) patients. A total of 60 PD patients were enrolled in this study, with a calcium content of the PD solution of 1.25 mmol/L in 30 patients (low-calcium group) and 1.75 mmol/L in 30 patients (standard-calcium group). Standard M-mode and two-dimensional ultrasound measurements were applied to detect the cardiac function. After 12-month follow-up, we found no significant difference in blood pressure, calcium, phosphorus, parathyroid hormone (PTH), etc., between the two groups. Residual renal function (RRF), which is associated with LV cardiac function, was significantly decreased in the standard-calcium group compared with the low-calcium group (5.64 ± 3.23 vs. 9.38 ± 3.17, \(p = .001\)). Compared with the low-calcium group, \(E_{\text{max}}\) (peak early diastolic velocity) and \(A_{\text{max}}\) (peak late diastolic velocity) were significantly decreased (\(p < .05\)), whereas myocardial performance index (MPI) was obviously increased in standard-calcium group (9.69 ± 2.71 vs. 7.75 ± 0.93, \(p < .05\)). In conclusion, our data suggest that low calcium dialysate treatment is significantly associated with better LV diastolic function.

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\section*{Introduction}

Left ventricular (LV) diastolic function was found to be a significant predictor of cardiovascular events and general mortality in hemodialysis.\textsuperscript{1} Numerous studies have proved that dialysate calcium concentration was significantly associated with cardiac function. Our previous study showed low calcium dialysate treatment was associated with reduced number of newly occurring cardiovascular events in peritoneal dialysis (PD) patients.\textsuperscript{2} Compared with lower calcium dialysate (1.25 or 1.5 mmol/L) treatment, standard calcium (1.75 mmol/L) dialysate impaired left ventricular (LV) cardiac function in hemodialysis (HD) and PD patients.\textsuperscript{3,4} Kim et al. indicated that LV diastolic dysfunction was a predictor of rapid decline of residual renal function (RRF) in PD patients.\textsuperscript{5} The decline of RRF induced extracellular fluid volume overload and hypertension, which resulted in myocardial hypertrophy.\textsuperscript{6} However, the relationship of low calcium dialysate and LV diastolic function has not been fully clear until now. In this study, we recruited 60 PD patients and followed up for 12 months, aimed to illuminate the influence of low calcium dialysate on cardiac function in PD patients.

\section*{Patients and methods}

This study was performed in a single center (Department of Nephrology, the Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, China). This study recruited PD patients from March 2011 to March 2013, who were newly treated with steady continuous ambulatory peritoneal dialysis (CAPD) for at least 3 months, but no more than 6 months. Exclusion criteria included were as follows: inflammatory disease, active malignancy, chronic liver disease, chronic obstructive airway disease, chronic rheumatic heart disease, congenital heart disease, serum calcium <1.8 mmol/L, and age <18 years or >70 years.
Patients were divided into two groups according to their admission order, one group received a solution of 1.25 mmol/L calcium (low-calcium group) PD solution, and the other group received a 1.75 mmol/L calcium (standard-calcium group) PD solution. The study was approved by the Ethics Committee of our Medical Faculty and written informed consent was obtained from all patients before study entry.

Fasting venous blood was collected for hemoglobin (Hb), high sensitivity CRP (hs-CRP), serum albumin (ALB), calcium (Ca), phosphorus (P), parathyroid hormone (PTH), cholesterol (CHOL), triglyceride (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). RRF is defined as the residual glomerular filtration rate (GFR) in patients with end stage renal disease (ESRD) and was estimated as the mean of renal urea and creatinine clearances. Total weekly urea clearance (Kt/V) and creatinine clearance (CCr) were measured every 4 weeks to detect the adequacy of dialysis in PD patients.

All echocardiographic examinations were performed by a single experienced sonographer, who was not aware of all clinical details. Standard M-mode and two-dimensional ultrasound measurements were applied in this study (APLIO ARTIDA, TOSHIBA, Japan). The following indices were measured: isovolumic relaxation time (IVRT), isovolumic contraction time (ICT), peak early diastolic velocity (E\text{max}), peak late diastolic velocity (A\text{max}), the ratio of peak early to peak late diastolic velocities (E/A\text{max}), ejection fraction (EF), and the index of myocardial performance (MPI). MPI was defined as (ICT + IVRT)/EF. Increment in IVRT, A\text{max}, and MPI and decrement in E\text{max} and E/A\text{max} < 1 were admitted as the indexes showing deterioration of left ventricular diastolic function.

Patients received treatment of standard PD dialysate from Baxter with high glucose degradation (GDPs), containing 3,4-DGE from 13 mmol/L to 20 mmol/L, sodium 132 mmol/L, calcium 1.25 or 1.75 mmol/L, magnesium 0.5 mmol/L, chlorine 96 mmol/L, lactate 40 mmol/L, and pH 5.2. We prescribed calcium carbonate, calcitriol, and sevelamer hydrochloride to maintain the target range of iPTH and normal calcium, phosphorus, and calcium–phosphorus product concentrations. Patients who suffered from peritonitis, exit site infections, other infective complications, or volume overload, all of the above assessments were delayed for at least 1 month following complete recovery.

**Statistical analyses**

All statistical analyses were done using SPSS 16.0 (SPSS Inc., Chicago, IL). Characteristics of the study patients are reported as means ± standard deviation for continuous variables, and as percentages or frequencies for categorical variables. One-way analysis of variance or nonparametric tests were used for the descriptive analysis or continuous variables. And Pearson’s chi-square test was used for categorical variables. \( p < .05 \) was considered statistically significant.

**Results**

**Baseline characteristics of CAPD patients in two groups**

In all, 65 patients were randomized, 33 to the low-calcium group (receiving a solution of 1.25 mmol/L calcium dialysate treatment) and 32 to standard-calcium group (receiving a solution of 1.75 mmol/L calcium dialysate treatment). Three patients in the low-calcium group and two patients in the standard-calcium group were dropout. Reasons for the dropout were as follows: transplantation \((n = 2)\), switch to hemodialysis \((n = 2)\), and transfer to other hospital \((n = 1)\). The causes of ESRD included chronic glomerulonephritis in 26 patients, diabetic nephropathy in 13 patients, hypertensive nephrosclerosis in 10 patients, tubulointerstitial nephritis in 5 patients, and unknown etiology in 6 patients. We compared baseline characteristics of 60 CAPD patients enrolled in the study. The average age was \(56.75 \pm 10.21\) years in the low-calcium group and \(54.15 \pm 7.75\) years in the standard-calcium group, male/female ratio was 13/17 and 16/14 in the low- and standard-calcium groups, respectively. No differences were found with respect to proportion of pre-existing DM, blood pressure, body mass index (BMI), RRF, total weekly urea clearance (Kt/V), creatinine clearance (CCr), and other clinical data between two groups (Table 1).

**Echocardiographic data of CAPD patients in two groups at baseline**

We compared baseline echocardiographic findings of 60 CAPD patients enrolled in the study. No differences were found with respect to IVRT, E\text{max}, A\text{max}, E/A\text{max}, MPI, and EF between two groups (Table 2).

**Standard calcium dialysate associated with decreased RRF level after 12-month follow-up**

After 12-month follow-up, RRF in the standard-calcium group was significantly decreased when compared to that in the low-calcium group \((p = .001\); Table 3). The change of RRF in standard-calcium group was obviously higher than that in low-calcium group.
group (p = .001; Table 4). However, we found no significant difference in blood pressure, BMI, calcium, phosphorus, iPTH, total Kt/V, CCr, and the other serum parameters in this study between the two groups. Moreover, two patients in low-calcium group and one patient in standard-calcium group who did not have DM history suffered from DM after 12-month follow-up (Table 3). We discovered that the decreased change of Kt/V in standard calcium was significantly higher than in low-calcium group (p < .05; Table 4).

**Echocardiographic data of CAPD patients in two groups after 12-month follow-up**

Compared with the low-calcium group, $E_{\text{max}}$ and $A_{\text{max}}$ were significantly decreased (p < .05), and MPI was obviously increased in standard-calcium group (p < .05). Increment in MPI and decrement in $E_{\text{max}}$ were admitted as the indexes showing deterioration of LV diastolic function. Furthermore, we found no significant differences in IVRT, E/A, and EF between the two groups (Table 5). And we discovered that the changes in the $E_{\text{max}}$, $A_{\text{max}}$, and MPI in standard-calcium group were more obvious than that in the low-calcium group (p < .05; Table 6).

**Discussion**

In this study, we found that RRF was significantly decreased in the standard-calcium group while compared with the low-calcium group. Moreover, compared with the low-calcium group, $E_{\text{max}}$ and $A_{\text{max}}$ were significantly decreased, and MPI was obviously increased in standard-calcium group. Our results suggested that low calcium dialysate treatment was significantly associated with better cardiac function.

CVD is the critical cause of mortality in PD and HD patients. Extracellular fluid volume overload and hypertension are the most common pathogenesis which result in myocardial hypertrophy. Calcium concentration was reported to be an important factor in the development of CVD. Silberberg et al. suggested that dialysate calcium concentrations were significantly associated with CVD in end stage renal disease (ESRD) patients. Kim et al. also found that low calcium dialysate obviously improved arterial stiffness parameters in
PD patients. Whether long-term low calcium dialysate could improve cardiac function has not been fully illuminated.

Dialysate calcium concentration is a crucial index in cardiac systolic and diastolic function. Compared to low calcium dialysate (Ca\(^{2+}\): 1.5 mmol/L or 1.25 mmol/L), high calcium dialysate (Ca\(^{2+}\): 1.75 mmol/L) impaired cardiac diastolic function in HD patients. Tuncer et al. enrolled 28 CAPD patients and altered dialysate calcium concentration from 1.75 mmol/L to 1.25 mmol/L for a month. They found that left ventricular relaxation was increased with the applying of low calcium dialysate. Kim and his colleagues enrolled 20 maintenance HD patients, and transferred dialysate calcium concentration from 1.75 mmol/L to 1.50 mmol/L at the beginning of the study, then patients were followed up for 6 months. Their results showed that low calcium dialysate significantly improved the arterial stiffness.

### Table 3. Clinical characteristics of patients between groups at 12-month follow-up.

|                      | Low-Ca group (n = 30) | Standard-Ca group (n = 30) | p Value* |
|----------------------|-----------------------|-----------------------------|----------|
| Age (years)          | 57.75 ± 10.21         | 55.15 ± 7.75                | .651     |
| Male man/woman       | 13/17                 | 16/14                       | .442     |
| Diabete              | 7                     | 9                           | .771     |
| Systolic BP (mmgh)   | 136.20 ± 12.78        | 134.40 ± 21.94              | .556     |
| Diastolic BP (mmgh)  | 79.70 ± 10.40         | 81.10 ± 13.93               | .689     |
| BMI (kg/m\(^2\))     | 23.51 ± 2.63          | 23.33 ± 1.95                | .867     |
| Hb (g/L)             | 115.75 ± 20.43        | 107.40 ± 18.34              | .256     |
| ALB (g/L)            | 36.67 ± 5.89          | 35.68 ± 6.38                | .613     |
| hs-CRP (mg/L)        | 10.27 ± 12.93         | 7.92 ± 13.82                | .581     |
| iPTH (pg/L)          | 36.68 ± 47.27         | 33.70 ± 38.34               | .831     |
| Ca (mmol/L)          | 2.39 ± 0.26           | 2.51 ± 0.33                 | .211     |
| P (mmol/L)           | 1.54 ± 0.39           | 1.68 ± 0.50                 | .526     |
| TC (mmol/L)          | 4.61 ± 0.97           | 4.56 ± 1.06                 | .894     |
| TG (mmol/L)          | 2.56 ± 1.03           | 2.13 ± 0.97                 | .340     |
| HDL (mmol/L)         | 0.93 ± 0.27           | 0.98 ± 0.22                 | .574     |
| LDL (mmol/L)         | 2.45 ± 0.78           | 2.61 ± 0.23                 | .523     |
| U/V (L/d)            | 446 ± 128             | 314 ± 132                   | .108     |
| UFV (L/24 h)         | 568 ± 189             | 612 ± 216                   | .412     |
| Total Kt/V urea/week | 2.01 ± 0.25           | 1.89 ± 0.4                  | .143     |
| Total Ccr/week/L/1.73m\(^2\) | 62.35 ± 21.35 | 59.42 ± 30.12 | .198 |

Ca: calcium; Low Ca: 1.25 mmol/L; Standard Ca: 1.75 mmol/L; BP: blood pressure; BMI: body mass index; Hb: hemoglobin; hs-CRP: high sensitivity C-reactive protein; ALB: serum albumin; P: phosphorus; PTH: parathyroid hormone; CHOL: cholesterol; TG: triglyceride; LDL: low-density lipoprotein; HDL: high-density lipoprotein; UV: urine volume; UFV: ultrafiltration volume; RRF: residual renal function. CCr: creatinine clearance.

*Standard dialysate versus low calcium dialysate.

### Table 4. Clinical characteristics changes between two groups.

|                      | Low-Ca group (n = 30) | Standard-Ca group (n = 30) | p Value* |
|----------------------|-----------------------|-----------------------------|----------|
| New-occurred diabetes| 2                     | 1                           | .549     |
| Systolic BP (mmgh)   | 22.70 ± 5.26          | 26.65 ± 14.89               | .556     |
| Diastolic BP (mmgh)  | 14.40 ± 2.62          | 9.90 ± 7.15                 | .689     |
| BMI (kg/m\(^2\))     | 1.14 ± 0.30           | 1.43 ± 0.24                 | .422     |
| Hb (g/L)             | 22.45 ± 3.15          | 21.05 ± 3.13                | .725     |
| ALB (g/L)            | 5.22 ± 0.95           | 7.76 ± 1.37                 | .138     |
| hs-CRP (mg/L)        | 2.31 ± 6.48           | 3.16 ± 6.35                 | .357     |
| iPTH (pg/L)          | 23.46 ± 6.98          | 22.30 ± 10.79               | .807     |
| Ca (mmol/L)          | 0.34 ± 0.042          | 0.27 ± 0.053                | .315     |
| P (mmol/L)           | 0.38 ± 0.075          | 0.41 ± 0.073                | .842     |
| TC (mmol/L)          | 1.22 ± 0.24           | 0.96 ± 0.22                 | .453     |
| TG (mmol/L)          | 4.18 ± 2.80           | 4.55 ± 2.81                 | .926     |
| HDL (mmol/L)         | 0.36 ± 0.061          | 0.24 ± 0.047                | .160     |
| LDL (mmol/L)         | 0.79 ± 0.16           | 0.77 ± 0.11                 | .927     |
| UV (L/d)             | 134 ± 62              | 145 ± 66                    | .343     |
| UFV (L/24 h)         | 114 ± 75              | 129 ± 86                    | .153     |
| RRF (ml/min)         | 1.02 ± 0.41           | 3.24 ± 1.03                 | .001     |
| Total Kt/V urea/week | 0.22 ± 0.032          | 0.42 ± 0.140                | .024     |
| Total Ccr/week/L/1.73m\(^2\) | 35.78 ± 14.58 | 40.16 ± 16.37 | .108 |

Ca: calcium; Low Ca: 1.25 mmol/L; Standard Ca: 1.75 mmol/L; BP: blood pressure; BMI: body mass index; Hb: hemoglobin; hs-CRP: high sensitivity C-reactive protein; ALB: serum albumin; P: phosphorus; PTH: parathyroid hormone; CHOL: cholesterol; TG: triglyceride; LDL: low-density lipoprotein; HDL: high-density lipoprotein; UV: urine volume; UFV: ultrafiltration volume; RRF: residual renal function. CCr: creatinine clearance.

*Standard dialysate versus low calcium dialysate.
Table 5. Echocardiographic findings in CAPD patients using standard or low calcium dialysate at baseline.

|                  | Low-Ca group (n = 30) | Standard-Ca group (n = 30) | p Valuea |
|------------------|-----------------------|---------------------------|----------|
| IVRT (ms)        | 87.25 ± 26.07         | 98.20 ± 25.64             | .189     |
| Emax (m/s)       | 0.71 ± 0.16           | 0.49 ± 0.20               | .001     |
| Amax (m/s)       | 1.00 ± 0.24           | 0.79 ± 0.27               | .016     |
| E/A              | 0.73 ± 0.20           | 0.69 ± 0.25               | .630     |
| MPI              | 7.75 ± 0.93           | 9.69 ± 2.71               | .004     |
| EF (%)           | 65.05 ± 3.45          | 65.80 ± 4.12              | .537     |

Ca: calcium; Low Ca: 1.25 mmol/L; Standard Ca: 1.75 mmol/L; IVRT: isovolumic relaxation time; Emax: peak early diastolic velocity; Amax: peak late diastolic velocity; E/A: the ratio of peak early to peak late diastolic velocities; MPI: myocardial performance index; EF: ejection fraction.

aStandard dialysate versus low calcium dialysate.

Table 6. Changes of echocardiographic findings in CAPD patients using standard or low calcium dialysate at baseline.

|                  | Low-Ca group (n = 30) | Standard-Ca group (n = 30) | p Valuea |
|------------------|-----------------------|---------------------------|----------|
| IVRT (ms)        | 19.55 ± 3.27          | 22.55 ± 3.37              | .527     |
| Emax (m/s)       | 0.112 ± 0.032         | 0.263 ± 0.029             | .001     |
| Amax (m/s)       | 0.123 ± 0.018         | 0.226 ± 0.025             | .045     |
| E/A              | 0.273 ± 0.043         | 0.303 ± 0.051             | .369     |
| MPI              | 2.48 ± 0.32           | 4.30 ± 0.52               | .005     |
| EF (%)           | 1.90 ± 0.25           | 2.05 ± 0.24               | .671     |

Ca: calcium; Low Ca: 1.25 mmol/L; Standard Ca: 1.75 mmol/L; IVRT: isovolumic relaxation time; Emax: peak early diastolic velocity; Amax: peak late diastolic velocity; E/A: the ratio of peak early to peak late diastolic velocities; MPI: myocardial performance index; EF: ejection fraction.

aStandard dialysate versus low calcium dialysate.

As it has been proved that aortic stiffness led to LV hypertrophy. Researchers assigned 30 patients on HD to be treated with dialysate calcium concentration of 1.12 or 1.37 mmol/L for 6 months. They found that higher dialysate calcium concentration was a risk factor for the progression of aortic stiffness in HD patients. Our previous study enrolled 40 PD patients, with dialysate calcium concentration of 1.25 mmol/L in 20 patients and 1.75 mmol/L in another 20 patients. After 12-month follow-up, low calcium dialysate treatment was associated with reduced number of newly occurring cardiovascular events in PD patients. Interestingly, it is reported that low calcium dialysate treatment for a month induced obviously decreasing level of serum calcium in PD patients. However, no difference was found in serum calcium levels between the two groups, after 12-month follow-up. Partly because these patients took calcium carbonate, calcitriol, and sevelamer hydrochloride to maintain the target range of iPTH, calcium, phosphorus, as well as calcium–phosphorus product concentrations.

Our echocardiographic findings showed that MPI was obviously changed and increased in standard-calcium group. MPI has been proved as a helpful systolic–diastolic index indicating the prognosis of patients who suffered from CVD. Lavine et al. indicated volume loading reduced MPI as a result of LV ejection time lengthening. But MPI did not changed because of heart rate incrementation or ageing. MPI was also used to assess the cardiac systolic function. EF showed no difference between low-calcium and standard-calcium groups, which indicated systolic function did not altered according to dialysate calcium concentration in this study. In that case, increment in MPI was admitted as the index indicating the impairment of LV diastolic function in PD patients. Our results confirmed that low calcium peritoneal dialysate maintained better LV diastolic function than standard calcium peritoneal dialysate in PD patients. Calcium has an important role in the contraction and relaxation of cardiac myocytes, in heart failure 3D organ models, elevated calcium level in diastolic period reduced abnormal residual diastolic force. In restrictive cardiomyopathy mouse model, calcium desensitizer catechin improved the diastolic function by reducing calcium hypersensitivity but not systolic function.

Moreover, our results indicate that standard calcium dialysate is associated with decreased RRF level and low calcium dialysate could keep the stability on RRF after 12-month follow-up. Kim et al. found that more than 80% ESRD patients had diastolic dysfunction, which might induce insufficiency of renal perfusion and lead to the decreasing of RRF. In this study, we noticed low calcium dialysate preserved RRF by maintaining LV diastolic function. Studies have showed that RRF had beneficial effects on LV hypertrophy and fluid removal. Loss of RRF led to fluid overload which enhanced the burden of LV and contributed to LV dysfunction. Wen et al. showed that higher peritoneal dialysate glucose concentration (PDGC) was significantly associated with low RRF and significantly associated with higher all-cause and CVD mortality. The rate of decline of RRF significantly associated with all-cause mortality in patients on long-term PD. To preserve RRF with low calcium dialysate should be a candidate strategy to lower CVD morbidity and mortality in PD patients.

There were some limitations in this study. First, this was a single-center study, and follow-up in the study was relatively short. Single-center study also had treatment bias. The applicability of our findings to the general PD population is therefore limited. Second, low GDP dialysate showed better preservation of RRF, we did not include the GDP ingredients (3,4-DGE) into our study parameters. To overcome the above-mentioned limitations, a prospective multicenter study with longer follow-up is warranted.

In conclusion, our data suggested that low calcium dialysate treatment was significantly associated with better LV diastolic function. Low calcium dialysate could
be a candidate strategy to reduce CVD mortality in CAPD patients.

Disclosure statement
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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