The Impact of A Reduction of Dialysate Calcium on Diastolic Function in Patients on Peritoneal Dialysis: A Prospective Study

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Abstract

Background

Cardiovascular disease is the main cause of death in patients on peritoneal dialysis (PD). The standard dialysate calcium content -d[Ca]- of 1.75mmol/L affects calcium balance, promoting calcium overload and impairing ventricular relaxation. Intracellular calcium handling might cause diastolic dysfunction (DD). We tested the hypothesis that reducing d[Ca] in patients on PD would improve DD.

Methods

d[Ca] was reduced from 1.75 mmol/L to 1.25 mmol/L. Two-dimensional speckle-tracking echocardiography was performed by a well-trained cardiologist at baseline and after 3 months. DD was determined according to the peak E-wave and peak A-wave velocities, wave deceleration time, and the duration of wave A. Diastolic function was normal, DD-1 (impaired ventricular relaxation), and DD-2 (restrictive pattern). Demographic, clinical, and biochemical parameters were evaluated.

Results

We included 19 patients (age 55 ± 17 years, 57.9% women, 21.1% diabetic, 84.2% on automatic PD). From baseline to 3 months, there was no change in any biochemical parameter. Left ventricular ejection fraction remained stable (from 58.4 ± 7.7 to 56.5 ± 8.1, p=0.192). Diastolic function classified at baseline as normal, DD-1 and DD-2 changed from 21.1%, 52.6% and 26.3–31.6%, 47.4% and 21.1% after 3 months, respectively, p=0.001). Increased filling pressure changed from 21.1–5.3% of patients (p=0.051).

Conclusions

Low d[Ca] could improve DD in patients on PD. This result might be related to a new set point of calcium myocardium homeostasis in these patients. Whether low d[Ca] may detain the development of heart failure and reduce cardiovascular in this population deserves further investigation.

Background

Patients with chronic kidney disease (CKD) have elevate rates of cardiovascular morbidity and mortality, attributable to traditional and nontraditional risk factors such as bone mineral disease and anemia [1]. Cardiovascular disease (CVD) is the main cause of death in patients with CKD, particularly in those on dialysis [2], reaching rates as high as 40-50% [3]. Although there have been a major technologic improvement in dialysis therapies, this population has a cardiovascular death rate 5-25 times higher than that observed in the general population [4].
Peritoneal dialysis (PD) allows continuous therapy that allows the maintenance of fluid, toxins and electrolyte balance, leading to the preservation of residual kidney function [5]. However, several PD-associated factors lead to an increased cardiovascular risk, mainly due to glucose overload, causing changes in the lipid profile, hyperinsulinemia and formation of advanced glycation end products [6]. The complex interaction between these risk factors causes a high prevalence of abnormalities of cardiac structure and function in patients with CKD [7].

Reliable and accessible tools that can early detect changes in cardiac function may facilitate the understanding and management of CVD in patients with CKD. In daily clinical practice, left ventricular ejection fraction (LVEF) is calculated with two-dimensional echocardiography, by measuring left ventricular end-diastolic and end-systolic volumes according to the biplane Simpson's method [8]. Despite a high prevalence of cardiovascular insults and progressive symptoms of heart failure, less than 15% of patients in dialysis have detectable systolic dysfunction [9, 10]. Hence, the majority of CKD patients will develop heart failure with preserved left ventricular function and different degrees of diastolic function [11–15].

Calcium (Ca) is a key messenger in the contraction of muscle, including the myocardium. At the myocyte level, changes in Ca homeostasis cause an increased diastolic cytosolic Ca, which leads to abnormalities in both active relaxation and passive stiffness. Ca is the central element of excitation-contraction coupling, so that hypercalcemia impairs the relaxation [16]. It has been described an association between serum Ca and ventricular end-diastolic diameter [17], and other parameters of myocardial relaxation [18]. In patients on hemodialysis, high dialysate calcium concentration (d[Ca]) causes an impairment in the diastolic function [19] and leads to a high incidence of myocardial infarction [20]. Several other studies have shown that d[Ca] plays an essential role in the physiology and pathology of cardiac dysfunction [6, 21].

The impact of the different d[Ca] in patients on peritoneal dialysis remains poorly evaluated. Hence, we tested the hypothesis that altering the d[Ca] from a standard to a lower concentration would decrease diastolic dysfunction (DD), quantified by two-dimensional STE, in patients on PD.

**Methods**

**Study Population and design of the study**

This was a single-center study in which patients were evaluated at baseline, using a standard 1.75 mmol/L d[Ca] and after switch to the 1.25 mmol/L d[Ca] for at least 3 months but no longer than 6 months. All prevalent patients on PD in the Institution were invited to participate. The inclusion criteria were patients >18 years old who were on PD for at least 6 months. Exclusion criteria were active episodes of decompensated heart failure or acute coronary syndrome, atrial fibrillation or another arrhythmia, and poor echocardiographic image quality. A total of 26 patients were selected after screening. After
exclusions due to arrhythmia (N=2), cardiac failure (N=2), and refusal to participate (N=3), the final sample included 19 patients.

The Local Institution Review Board at the Hospital da Clinicas da Universidade de São Paulo (Cappesq# 30284714.0.0000.0068) has approved the study protocol, which was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent to participate in the study.

**Laboratory Measurements**

Biochemical analysis was performed at baseline and 3 months after the d[Ca] has changed. All biochemical analyses were done according to standard techniques and included: hemoglobin (Reference range – RR: 13.5-17.5 g/dl for men and 12.0-15.5 g/dl for women), total Ca and phosphate (P) (RR 8.4 - 10.2 mg/dl, and 2.7- 4.5 mg/dl, respectively), ionized Ca (RR 4.73-5.29 mg/dl), alkaline phosphatase (AP) (RR 35-104 U/L in women and 40-129 U/L in men), troponin (RR < 0.03 ng/mL), 25OH-vitamin D (RR 30 - 100 ng/ml), and brain natriuretic peptide (BNP – RR < 70 pg/mL). Parathyroid hormone (PTH) was measured by chemiluminescence immunoassay (RR 11–65 pg/mL; Roche immunoassay analyzer, Roche Diagnostics, Germany), and fibroblast growth factor 23 (FGF-23) was measured by ELISA (immutopics, San Clemente, CA, USA).

**Bioimpedance Analysis (Bia)**

The multi-frequency segmental BIA was performed using the InBody 720® equipment (Biospace Co, Ltd, Seoul, Korea). The measurement was performed at baseline and 3 months after the intervention.

This device evaluates the amount of intracellular and extracellular body water in the different segments of the body, through the passage of an alternating electric current at different frequencies detected by electrodes that are placed on the ankles and hands. This technique was previously validated (accuracy of 0.5% and repeatability 0.3%) [22] for measurements of body fluids and has a close correlation with the gold standard of volume assessment in dialysis patients, as methods of diluting markers (Deuterium and sodium bromide) or magnetic resonance imaging [23].

The procedure was performed with the patient in the supine position. Electrodes were placed on the ankles and hands (first and third fingers) according to the manufacturer’s manual. The patient was instructed to remove metal objects and to remain in a comfortable position and as immobile as possible.

The parameters evaluated were total body water (TBW), extracellular water (ECW), intracellular water (ICW), and the TBW/ECW ratio (normal values are between 0.36 to 0.39, ≥ 0.40 indicates hypervolemia).

**Echocardiographic Measurements**
An experienced cardiologist blinded to the study group performed and analyzed all exams. Two-dimensional echocardiography was performed in the left lateral decubitus position in both experimental situations (d[Ca] 1.75 and 1.25 mmol/L). The cardiologist obtained the following echocardiography images: the standard apical 2-, 3- and 4-chamber views. The images were obtained (1.5–3.6 MHz 3 S probe, Vivid I; GE Medical Systems, Sonigen, Germany).

Images and parameters were evaluated according to the American Society of Echocardiography. The LVEF was calculated using Simpson's biplane method. Left ventricular mass index was determined as the ratio of left ventricular mass to body surface area. Left ventricular hypertrophy (LVH) was present when index mass was > 116 g/m$^2$ for men and > 96 g/m$^2$ for women [24].

Presence of diastolic dysfunction was determined after evaluating the following parameters: peak E-wave velocity (cm/sec), peak A-wave velocity (cm/sec), wave deceleration time (wave E), and duration of wave A. Diastolic function was then classified into 1 of 4 categories: normal, alteration of left ventricular relaxation, pseudo normal pattern, and restrictive pattern (reversible and irreversible) according to previous guidelines established by the American Society of Echocardiography and the European Association of Cardiovascular Imaging [24, 25]. DD refers to impaired left ventricular filling capacity due to abnormalities in relaxation or stiffness of the myocardium. The reference ranges for the structural and functional echocardiography variables used to assess DD have been derived from studies employing transthoracic echocardiography parameters.

**Statistical analysis**

The results are presented as the mean ± SD or median and (25–75) quartiles depending on the normality of the data. Comparisons between continuous variables while using D[Ca] 1.75 and D[Ca] 1.25 mmol/L were done using paired t-test or Wilcoxon test according to the Gaussian distribution. We used the McNemar test to compare categorical variables before and after the intervention. Correlations between independent variables were tested by Spearman coefficients.

A p-value < 0.05 was considered significant. Analyses were performed with the use of SPSS 21.0 (SPSS Inc., Chicago, Ill., USA) and GraphPad Prism® software version 9.0 (GraphPad Software, Inc., Calif., USA).

**Results**

A total of 19 were included in the study and 16 (84.2%) were in automated PD. They aged 55 ± 17 years, (11 women, 57.9%), and were on PD for a median time of 10.4 (3.7, 17.0) months. Primary kidney disease was chronic glomerulonephritis in 12 patients (63.1%), hypertension in 2 patients (10.5%), diabetes in 4 patients (21.1%), and adult polycystic kidney disease in 1 patient (5.3%). Previous cardiovascular events were identified in 3 patients (15.8%) and most of the patients were treating systemic hypertension (68.4%). At the study entry systolic and diastolic blood pressure were 128.8 ± 21.3 and 76.0 ± 12.5 mmHg, respectively. Anti-hypertensive medication in use included β-blocker (42.1%), calcium antagonist
(3.8%), and angiotensin-converting enzyme inhibitors or block aldosterone receptor blocker (ACE/ARB) (57.9%). Residual diuresis was 1,307 ml (from 400 to 2,160 ml). One patient was anuric. During the follow-up, the doses of antihypertensive medication did not change, and blood pressure levels remain stable for both systolic (p=0.468) and diastolic (p=0.363) levels.

Table 1 shows laboratory and body composition changes from pre- to post-d[Ca] change. During the follow-up, diuresis volume reduced.

| Table 1 | Laboratorial and body composition changes pre and post intervention. |
|---------|---------------------------------------------------------------|
| Variable | 1.75 mmol/L d[Ca] | 1.25 mmol/L d[Ca] | p     |
|----------|------------------|------------------|-------|
| Hemoglobin, g/dl | 11.6 ± 1.6 | 11.2 ± 1.4 | 0.245 |
| Total calcium, mg/dl | 9.1 ± 0.7 | 9.1 ± 1.1 | 1.0   |
| Ionized calcium, mg/dl | 4.89 ± 0.3 | 4.75 ± 0.5 | 0.182 |
| Phosphate, mg/dl | 4.7 ± 1.0 | 5.1 ± 0.6 | 0.104 |
| PTH, pg/ml | 419 (136, 921) | 393.4 (145, 843) | 0.678 |
| Alkaline phosphatase, U/L | 82 (61, 116) | 80 (60, 140) | 0.477 |
| 25 (OH) vitamin D, ng/mL | 24.7 ± 7.3 | 30.7 ± 11.5 | 0.064 |
| BNP, pg/mL | 1,050 (481, 2,216) | 1,091 (784, 3,994) | 0.198 |
| Troponin, ng/mL | 0.029 ± 0.019 | 0.034 ± 0.019 | 0.224 |
| Diuresis, ml | 1,219 ± 601 | 1,053 ± 716 | 0.021 |
| Ultrafiltration, mL | 809 ± 383 | 825 ± 410 | 0.721 |
| Extracellular water, L | 14.5 ± 3.0 | 14.6 ± 3.3 | 0.767 |
| ECW/TBW, L | 0.392 ± 0.023 | 0.394 ± 0.026 | 0.699 |
| Intracellular water, L | 21.3 ± 4.9 | 21.5 ± 5.6 | 0.576 |
| Total body water, L | 34.3 ± 10.5 | 34.6 ± 11.2 | 0.663 |

Data expressed as mean ± SD, median (25,75). PTH, parathyroid hormone; BNP, brain natriuretic peptide; ECW, extracellular water; TBW, total body water

Echocardiographic parameters are shown in Table 2. At baseline 10 out of 19 patients (52.6%) had LVH. After 3 months LVH was detected in 2 more patients (63.2%). Systolic function was within the normal range in most patients (63.15%). After changing the d[Ca] there were no structural changes detected in both left and right chambers, and in the pulmonary pressure. In addition, left ventricular systolic function was maintained. However, significant alterations were detected in left ventricular filling pressure in some
patients, which led to a decreased in the percentage and in the grade of DD, as shown in Table 2 and Figure 1.
Table 2
Echocardiographic changes pre and post reduction of dialysate calcium concentration from 1.75 to 1.25 mmol/L.

| Parameter                                      | 1.75 d[Ca] mmol/L | 1.25 d[Ca] mmol/L | p   |
|-----------------------------------------------|-------------------|-------------------|-----|
| **Left cameras structure and systolic function** |                   |                   |     |
| N= 19                                         | N=19              |                   |     |
| LVDD, mm                                      | 48.2 ± 6.5        | 48.5 ± 5.9        | 0.753 |
| LVSD, mm                                      | 31.7 ± 6.5        | 31.3 ± 5.7        | 0.406 |
| LV hypertrophy, n (%)                         | 10 (52.6)         | 12 (63.2)         | 0.500 |
| Interventricular septum, mm                   | 11.2 ± 2.3        | 11.0 ± 1.8        | 0.677 |
| Posterior wall thickness, mm                  | 10.8 ± 1.9        | 10.9 ± 1.7        | 0.822 |
| Left atrium, mm                               | 41.4 ± 6.7        | 42.6 ± 6.8        | 0.111 |
| ERP,                                          | 0.454 ± 0.068     | 0.453 ± 0.066     | 0.942 |
| LVIM, mm                                      | 116.6 ± 39.5      | 114.6 ± 27.2      | 0.841 |
| LVEF (Simpson), %                             | 58.4 ± 7.7        | 56.5 ± 8.1        | 0.192 |
| < 40%, n (%)                                  | 1 (5.3)           | 1 (5.3)           |     |
| 40-55%, n (%)                                 | 4 (21.1)          | 8 (42.1)          |     |
| > 55%, n (%)                                  | 14 (73.7)         | 10 (52.6)         |     |
| **Left ventricular diastolic function**       |                   |                   |     |
| IVRT, ms                                      | 113.3 ± 22.7      | 116.1 ± 19.6      | 0.670 |
| DT, ms                                        | 222.4 ± 86.6      | 216.1 ± 80.1      | 0.556 |
| E wave velocity (cm/s)                        | 0.663 ± 0.22      | 0.655 ± 0.18      | 0.896 |
| E/A Ratio                                     | 1.174 ± 0.64      | 1.126 ± 0.55      | 0.441 |
| Diastolic dysfunction, n (%)                  | 4 (21.1)          | 6 (31.6)          | 0.001 |
| Without dysfunction                            | 10 (52.6)         | 9 (47.4)          |     |
| Grade 1 dysfunction                           | 5 (26.3)          | 4 (21.1)          |     |
| Dysfunction ≥ 2                               |                   |                   |     |

Data expressed as mean ± SD, median (25,75) unless otherwise specified. BNP, brain natriuretic peptide; ECW, extracellular water; TBW, total body water; LVDD, left ventricular diastolic diameter; LVSD, left ventricular systolic diameter; RWT, relative wall thickness; LVIM, left ventricular index mass; LVEF, left ventricular ejection fraction; IVRT, isovolumetric relaxation time; DT, deceleration time E/A ratio: the ratio of peak early to peak late diastolic velocities; RA, right atrium; S’, tissue doppler of the free lateral wall; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle; SPPA, systolic pressure in the pulmonary artery.
### Discussion

In the present study, we demonstrated a better diastolic cardiac function in response to a decrease in d[Ca] from 1.75 to 1.25 mmol/L in patients on PD. This result was independent of the serum calcium concentration, which did not change. The improvement of diastolic echocardiographic parameters may be related to a new set point of calcium myocardium homeostasis in these patients. We can speculate that improvement of left ventricular relaxation mediated by low d[Ca] might detain the development of heart failure in dialytic patients.

Sidney Ringer discovered in the 1880s that Ca is essential for the heart’s contraction, and many roles of Ca in the cell continue to astonish us. Maintaining serum Ca at physiological levels is especially important for several biological processes, including vascular tone, muscle contractility, and stimulus...
conduction activity in the nervous system. The myocardium uses Ca in a positive feedback loop to trigger contraction. Indeed, Ca is a crucial element in cardiac systolic and diastolic function [6] and hypercalcemia impairs especially myocardium relaxation [16]. Therefore, there might be a link between high Ca concentration, worse ventricular relaxation, DD, and the development of clinical manifestation of heart failure with preserved LVEF.

The prevalence of DD is becoming more frequent than systolic dysfunction [26]. According to a recent systematic review, DD affects approximately 36% of the population older than 60 years [27]. Importantly, not all patients with DD develop clinical heart failure. Diastolic heart failure occurs more often in heart failure with an LV ejection fraction of more than 50% [28]. DD is associated with a 3.53-fold higher risk of combined events of MACE and death and a 3.13-fold increased risk of death [26]. Patients with CKD have a high burden of cardiovascular risk factors closely related to accelerated atherosclerosis, left ventricular dilatation with hypertrophy, systolic dysfunction, and high left ventricular filling pressure [29]. In line with these findings, most of our patients were hypertensive and had LVH and, although EF was normal in 63.15%, DD was found in 78.9% of cases.

Pathophysiological changes that lead to DD have a deleterious impact on cardiac function. Hypertension, obesity, hypercholesterolemia, and diabetes are associated with systemic inflammation, myocardial oxidative stress, and coronary microvascular dysfunction, common risk factors for cardiovascular disease, contributing to myocardial stiffening and left ventricular DD [30]. As explained by Ogawa and Nitta [31], the central mechanism of left ventricular DD is LVH with myocardial interstitial fibrosis, which induces myocardial stiffness and impairs heart function during diastole. In patients with CKD, congestive heart failure is caused by LVH due to arterial hypertension and chronic anemia. Left ventricular DD causes an increase in left ventricular filling pressure, which may lead to pulmonary congestion. The severity of CKD is the most independent predictor of elevated left ventricular filling pressure and might be responsible for systolic and diastolic dysfunction in patients with CKD not on dialysis [32]. The prevalence and severity of LVH increase as the CKD progresses, according to Levin et al.[33]. Structural changes combined with anemia and hyperparathyroidism promote maladaptive LVH, leading to systolic and DD [34].

Echocardiography, a non-invasive technique, allows the assessment of multiple indices of diastolic function, with good concordance with invasive hemodynamic monitoring [29, 35]. However, no single echocardiographic parameter is considered sufficiently accurate and reproducible to establish the diagnosis of DD [36]. DD is difficult to characterize, and refers to abnormal mechanical properties of the myocardium, including abnormal LV diastolic distensibility, impaired filling, and slow or delayed relaxation, regardless of whether the EF is normal or depressed and regardless the presence of symptoms [37]. Since DD implies that the myofibrils do not rapidly or entirely return to their resting length, the ventricle cannot accept blood at low pressures [34]. In this situation, the ventricular filling is slow or inadequate unless there is an increase in the atrial pressure [38]. Consequently, there is an increased dependence on filling through the atrial contraction and higher atrial pressures to maintain filling or cardiac output [38]. These parameters were improved in our patients after a reduction in the d[Ca],
suggesting that lower d[Ca] improved diastolic function in patients on PD. During diastole, the left ventricle, the left atrium, and the pulmonary veins form a common chamber continuous with the pulmonary capillary bed [39]. In late diastole, the ventricle is most compliant and easily distensible, offering minimal resistance to ventricular filling over a normal volume range [39]. The active phase is myocyte dependent and relies on the rapid decline in [Ca2+] at the beginning of diastole, leading to dissociation of the thick and thin filaments. In the subsequent passive phases of diastole, the pressure gradient distends the ventricle [40].

The importance of d[Ca] in patients on dialysis and its correlation with cardiac function has been gaining ground in recent years. Most studies, however, included patients on hemodialysis. Usually, patients on PD dialyze against high d[Ca], 1.75mmol/L [6, 38, 39]. The influence of d[Ca] in cardiovascular risk as well as in systolic and diastolic function in patients on PD has been demonstrated. Liang et al. have shown that low d[Ca] is associated with a reduced number of newly occurring cardiovascular events [40]. Wang et al. have suggested that d[Ca] was associated with a better cardiac function [41]. Standard 1.75 mmol/L D[Ca] impaired left ventricular cardiac function in patients on PD [18]. Kim et al. have also found that low d[Ca] improved arterial stiffness parameters in patients on PD [42]. Whether long-term low d[Ca] could improve cardiac function has not been fully addressed. Tuncer et al. have shown an improvement of LV relaxation by reducing d[Ca] from 1.75 mmol/L to 1.25 mmol/L for only a month in patients on continuous ambulatory PD [18].

Our results need to be interpreted considering some limitations: it was a single-center study that included a small number of patients, with a short follow-up. Although the precise prevalence rate of diastolic heart failure in PD patients is unknown, a higher prevalence of left ventricular diastolic heart failure in patients with CKD than in the general population is expected in light of the occurrence of inflammation, fluid overload, hypertension, renin-angiotensin-aldosterone system activation, and LVH [43]. Strengths of our study rely upon having included patients on automatic PD, the most applied technique nowadays, echocardiography was performed by the same expert observer, and the same researcher followed all patients during the study.

**Conclusions**

In conclusion, we demonstrated that low d[Ca] was associated with better left ventricular diastolic function suggesting that this dialysate could be a candidate strategy to reduce CVD mortality in PD patients.

**Abbreviations**

**PD**: peritoneal dialysis

**DD**: diastolic dysfunction

**CKD**: chronic kidney disease
CVD: cardiovascular disease
LVEF: left ventricular ejection fraction
Ca: Calcium
P: phosphate
BNP: brain natriuretic peptide
AP: alkaline phosphatase
PTH: parathyroid hormone
FGF-23: fibroblast growth factor 23
BIA: bioimpedance analysis
TBW: total body water
ECW: extracellular water
ICW: intracellular water
LVH: left ventricular hypertrophy
ACE: angiotensin converting enzyme
ARB: aldosterone receptor blocker

Declarations

Ethics approval and consent to participate

Study approval statement: The Local Institution Review Board at the Hospital das Clínicas da Universidade de São Paulo (Cappesq# 30284714.0.0000.0068) has approved the study protocol, which was conducted in accordance with the Declaration of Helsinki.

Consent to participate statement: All participants provided written informed consent to participate in the study.

Consent for publication

Not applicable in the declarations

Availability of data and materials
All data supporting the findings of this study are available within the article. Raw data are available at https://www.scidb.cn/en/datalist.

**Competing interests**

The authors have no conflicts of interest to declare.

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**Authors' contributions**

The authors contributions were as follows: 1. Conception or design, or analysis and interpretation of data, or both: MCTP, TAM, RME; 2. Drafting the article or revising it: MCTP, FMC, RME; 3. Providing intellectual content of critical importance to the work described: FMC, RMAM, FMC, RME; 4. Final approval of the version to be published: MCTP, TAM, EAG, HA, BJP, FMC, RMAM, RME

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**References**

1. Garcia-Lopez E, Carrero JJ, Suliman ME, Lindholm B, Stenvinkel P: Risk factors for cardiovascular disease in patients undergoing peritoneal dialysis. *Perit Dial Int* 2007, **27** Suppl 2:S205-209.

2. Vazquez E, Sanchez-Perales C, Garcia-Garcia F, Garcia-Cortes MJ, Torres J, Borrego F, Salas D, Liebana A, Fernandez-Guerrero JC: Sudden death in incident dialysis patients. *Am J Nephrol* 2014, **39**(4):331-336.

3. Zhe XW, Zeng J, Tian XK, Chen W, Gu Y, Cheng LT, Chen HM, Axelsson J, Lindholm B, Wang T: Pulse wave velocity is associated with metabolic syndrome components in CAPD patients. *Am J Nephrol* 2008, **28**(4):641-646.

4. Foley RN, Parfrey PS, Sarnak MJ: Epidemiology of cardiovascular disease in chronic renal disease. *J Am Soc Nephrol* 1998, **9**(12 Suppl):S16-23.

5. Bargman JM, Thorpe KE, Churchill DN, Group CPDS: Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. *J Am Soc Nephrol* 2001, **12**(10):2158-2162.
6. Wang AY, Brimble KS, Brunier G, Holt SG, Jha V, Johnson DW, Kang SW, Kooman JP, Lambie M, McIntyre C et al: ISPD Cardiovascular and Metabolic Guidelines in Adult Peritoneal Dialysis Patients Part I - Assessment and Management of Various Cardiovascular Risk Factors. *Perit Dial Int* 2015, 35(4):379-387.

7. Foley RN, Parfrey PS, Sarnak MJ: Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998, 32(5 Suppl 3):S112-119.

8. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T et al: Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015, 16(3):233-270.

9. Stallworthy EJ, Pilmore HL, Webster MW, Sidhu KK, Curry EM, Brown P, Scaria A: Do echocardiographic parameters predict mortality in patients with end-stage renal disease? *Transplantation* 2013, 95(10):1225-1232.

10. Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, Barre PE: Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 1995, 47(1):186-192.

11. Edwards NC, Hirth A, Ferro CJ, Townend JN, Steeds RP: Subclinical abnormalities of left ventricular myocardial deformation in early-stage chronic kidney disease: the precursor of uremic cardiomyopathy? *J Am Soc Echocardiogr* 2008, 21(12):1293-1298.

12. Hayashi SY, Rohani M, Lindholm B, Brodin LA, Lind B, Barany P, Alvestrand A, Seeberger A: Left ventricular function in patients with chronic kidney disease evaluated by colour tissue Doppler velocity imaging. *Nephrol Dial Transplant* 2006, 21(1):125-132.

13. Park M, Hsu CY, Li Y, Mishra RK, Keane M, Rosas SE, Dries D, Xie D, Chen J, He J et al: Associations between kidney function and subclinical cardiac abnormalities in CKD. *J Am Soc Nephrol* 2012, 23(10):1725-1734.

14. de Bie MK, Ajmone Marsan N, Gaasbeek A, Bax JJ, Groeneveld M, Gabreels BA, Delgado V, Rabelink TJ, Schalij MJ, Jukema JW: Left ventricular diastolic dysfunction in dialysis patients assessed by novel speckle tracking strain rate analysis: prevalence and determinants. *Int J Nephrol* 2012, 2012:963504.

15. Shlipak MG, Lash JP, Yang W, Teal V, Keane M, Cappota T, Keller C, Jamerson K, Kusek J, Delafontaine P et al: Symptoms characteristic of heart failure among CKD patients without diagnosed heart failure. *J Card Fail* 2011, 17(1):17-23.

16. Virtanen VK, Saha HH, Groundstroem KW, Seppala ES, Pasternack Al: Calcium infusion and left ventricular diastolic function in patients with chronic renal failure. *Nephrol Dial Transplant* 1998, 13(2):384-388.

17. Poudel K, Shah AM, Michos ED, Folsom AR, Konety S, Lutsey PL: Association of serum calcium and phosphorus with measures of left ventricular structure and function: The ARIC study. *Nutr Metab*
18. Tuncer M, Ermis C, Suleymanlar G, Yakupoglu G, Ersoy FF: Low calcium dialysate increases cardiac relaxation in CAPD patients. *Perit Dial Int* 2002, 22(6):714-718.

19. Nappi SE, Saha HH, Virtanen VK, Mustonen JT, Pasternack AI: Hemodialysis with high-calcium dialysate impairs cardiac relaxation. *Kidney Int* 1999, 55(3):1091-1096.

20. Tagawa M, Hamano T, Sueta S, Ogata S, Saito Y: Higher dialysate calcium concentration is associated with incident myocardial infarction among diabetic patients with low bone turnover: a longitudinal study. *Sci Rep* 2018, 8(1):10060.

21. Vassalle M, Lin CI: Calcium overload and cardiac function. *J Biomed Sci* 2004, 11(5):542-565.

22. Demura S, Sato S, Kitabayashi T: Percentage of total body fat as estimated by three automatic bioelectrical impedance analyzers. *J Physiol Anthropol Appl Human Sci* 2004, 23(3):93-99.

23. Singh A, Ward RP: Appropriate Use Criteria for Echocardiography: Evolving Applications in the Era of Value-Based Healthcare. *Curr Cardiol Rep* 2016, 18(9):93.

24. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T et al: Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015, 28(1):1-39 e14.

25. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P et al: Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016, 29(4):277-314.

26. Ladeiras-Lopes R, Araujo M, Sampaio F, Leite-Moreira A, Fontes-Carvalho R: The impact of diastolic dysfunction as a predictor of cardiovascular events: A systematic review and meta-analysis. *Rev Port Cardiol* 2019, 38(11):789-804.

27. van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH: Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. *Eur J Heart Fail* 2016, 18(3):242-252.

28. Chinnaiyan KM, Alexander D, Maddens M, McCullough PA: Curriculum in cardiology: integrated diagnosis and management of diastolic heart failure. *Am Heart J* 2007, 153(2):189-200.

29. Kasner M, Westermann D, Steendijk P, Gaub R, Wilkenshoff U, Weitmann K, Hoffmann W, Poller W, Schultheiss HP, Pauschinger M et al: Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative Doppler-conductance catheterization study. *Circulation* 2007, 116(6):637-647.

30. Sorop O, Heinonen I, van Kranenburg M, van de Wouw J, de Beer VJ, Nguyen ITN, Octavia Y, van Duin RWB, Stam K, van Geuns RJ et al: Multiple common comorbidities produce left ventricular diastolic dysfunction associated with coronary microvascular dysfunction, oxidative stress, and myocardial stiffening. *Cardiovasc Res* 2018, 114(7):954-964.
31. Ogawa T, Nitta K: Clinical Impact of Left Ventricular Diastolic Dysfunction in Chronic Kidney Disease. *Contrib Nephrol* 2018, **195**:81-91.

32. Hung MJ, Yang NI, Wu IW, Cheng CW, Liu PC, Chen SJ, Wu MS, Cherng WJ: Three-dimensional echocardiographic assessment of left ventricular remodeling in predialysis chronic kidney disease patients. *J Nephrol* 2012, **25**(1):96-106.

33. Levin A, Singer J, Thompson CR, Ross H, Lewis M: Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention. *Am J Kidney Dis* 1996, **27**(3):347-354.

34. Gaasch WH, Zile MR: Left ventricular diastolic dysfunction and diastolic heart failure. *Annu Rev Med* 2004, **55**:373-394.

35. Combes A, Arnoult F, Trouillet JL: Tissue Doppler imaging estimation of pulmonary artery occlusion pressure in ICU patients. *Intensive Care Med* 2004, **30**(1):75-81.

36. Ladeiras-Lopes R, Araujo M, Sampaio F, Leite-Moreira A, Fontes-Carvalho R: The impact of diastolic dysfunction as a predictor of cardiovascular events: A systematic review and meta-analysis. *Rev Port Cardiol (Engl Ed)* 2019, **38**(11):789-804.

37. Deswal A: Diastolic dysfunction and diastolic heart failure: mechanisms and epidemiology. *Curr Cardiol Rep* 2005, **7**(3):178-183.

38. Weissheimer R, Bucharles SGE, Truyts CAM, Jorgetti V, Figueiredo AE, Barrett P, Olandoski M, Pecoits-Filho R, Moraes TP: High prevalence of biochemical disturbances of chronic kidney disease - mineral and bone disorders (CKD-MBD) in a nation-wide peritoneal dialysis cohort: are guideline goals too hard to achieve? *J Bras Nefrol* 2021.

39. Sanchez C, Lopez-Barea F, Sanchez-Cabezudo J, Bajo A, Mate A, Martinez E, Selgas R, Multicentre Study Group C: Low vs standard calcium dialysate in peritoneal dialysis: differences in treatment, biochemistry and bone histomorphometry. A randomized multicentre study. *Nephrol Dial Transplant* 2004, **19**(6):1587-1593.

40. Liang J, Wang Z, Liu G, Zhan J, Jiang L, Jiang Z: Association of dialysate calcium concentration with fetuin A level and carotid intima-media thickness in peritoneal dialysis patients. *Ren Fail* 2014, **36**(1):65-68.

41. Wang Z, Wen Y, Liang J, Liang X, Shi W: The influence of low calcium dialysate on left ventricular diastolic function in peritoneal dialysis patients. *Ren Fail* 2016, **38**(10):1665-1671.

42. Kim JK, Moon SJ, Park HC, Lee JS, Sim SR, Bae SC, Ha SK: Effects of lowering dialysate calcium concentrations on arterial stiffness in patients undergoing hemodialysis. *Korean J Intern Med* 2011, **26**(3):320-327.

43. Wu CK, Huang YT, Lin HH, Yang CY, Lien YC, Lee JK, Huang JW, Hung KY: Dissecting the mechanisms of left ventricular diastolic dysfunction and inflammation in peritoneal dialysis patients. *PLoS One* 2013, **8**(5):e62722.
Cross tabulation of filling pressure and diastolic function at baseline and post-intervention.

Figure 1