

**Original Paper**

# Nonparallel Progression of Left Ventricular Structure and Function in Long-Term Peritoneal Dialysis Patients

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**Keywords**

Left ventricular structure · Systolic function · Diastolic function · Peritoneal dialysis

**Abstract**

**Background/Aims:** Left ventricular hypertrophy and dysfunction are key cardiovascular risk factors of patients on peritoneal dialysis (PD). The purpose of this study was to investigate the dynamic changes of left ventricular (LV) structure and function in patients on long-term PD. **Methods:** Patients who underwent PD catheter insertions from January 2010 to December 2012 in our PD center were enrolled into this study. Cardiac structure and function of those patients were determined by echocardiography (4 times) at 12-month intervals. Patients' biochemical parameters, body mass index, blood pressure, urine output, ultrafiltration, and total fluid removal volume were collected. The use of antihypertensive drugs and active vitamin D<sub>3</sub> was also recorded. **Results:** A total of 40 patients were included. After 3 years of follow-up, patients' PD duration time, LV mass/height<sup>2.7</sup> ( $p = 0.580$ ), interventricular septal thickness ( $p = 0.216$ ), left ventricular posterior wall thickness ( $p = 0.216$ ), and LV ejection fraction ( $p = 0.270$ ) did not show significant changes during the follow-up. In contrast, the E/A ratio ( $p = 0.004$ ) and  $e'$  ( $p < 0.001$ ) were statistically decreased, and the E/ $e'$  ratio ( $p = 0.006$ ) was increased. Left atrial diameter was increased ( $p = 0.008$ ), but the changes in left atrial diameter index did not reach statistical significance ( $p = 0.090$ ). **Conclusion:** Long-term PD patients maintain stable LV structure and cardiac systolic function, but cardiac diastolic function declines over time.

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## Introduction

Cardiac structural and functional changes are the most prevalent cardiovascular risks in chronic kidney disease (CKD), accounting for nearly 50% of the mortality in dialysis patients [1, 2]. Cross-section surveys demonstrate that up to 80% of dialysis patients have left ventricular (LV) alterations, among which left ventricular hypertrophy (LVH) is the most frequent finding [3]. LVH is considered a key cardiovascular complication in peritoneal dialysis (PD) patients, with an estimated prevalence ranging from 44 to >90% [4].

Studies of the impact of hemodialysis on LV systolic function have reported mixed results. A 10-year survey by Paoletti et al. [5] demonstrated that LVH was progressive and continued after the initiation of dialysis treatment. Assa et al. [6] demonstrated that LV diastolic function worsened early during a hemodialysis session. So far, research conducted in PD patients has been limited and usually performed with a small sample size and short follow-up duration. A recent study suggested that hypotension was more likely to cause cardiac structure and function deterioration than hypertension in PD patients [7]. However, hypotension is an ill-defined condition and its incidence is considered low in PD patients; moreover, that study did not involve other factors that may be associated with cardiac structure and function, except for blood pressure (BP).

We conducted a retrospective study to analyze the dynamic changes of LV structure and function in long-term PD patients followed up for 3 years. The follow-up period was relatively long, and we performed a more comprehensive analysis including LV structure as well as LV diastolic and systolic function. We also explored the mechanisms underlying the long-term changes in LV structure and function by examining the differences in risk factors associated with LV structure and function. Traditional and nontraditional factors such as BP, volume control, dialysis duration time, serum phosphorus, and parathyroid hormone (PTH) were analyzed.

## Subjects and Methods

### *Study Subjects*

There were 121 patients who underwent PD catheter insertion in our PD center from January 2010 to December 2012. All patients received continuous ambulatory PD initially and none of them was transferred from hemodialysis. Each patient's dwell volume was 2 L. Patients who were aged >18 years and who received echocardiographic examinations 4 times were included in the study. The first examination was done during the catheterization period, and the last 3 assessments were performed every 12 months during the 3-year follow-up period. A total of 69 patients eventually finished the whole examinations. No serious cardiovascular adverse events occurred in these patients during the follow-up, but 29 subjects were excluded. The exclusion criteria included unsatisfactory echocardiographic images ( $n = 10$ ), renal transplantation during the follow-up period ( $n = 2$ ), transfer to hemodialysis ( $n = 6$ ), combined therapy with PD and hemodialysis ( $n = 4$ ), recovery of renal function ( $n = 1$ ), congenital heart disease ( $n = 1$ ), rheumatic heart disease ( $n = 1$ ), and acute inflammatory diseases ( $n = 4$ ). Thus, the total number of patients included in this study was 40.

### *Study Methods*

The clinical data collected included age, gender, catheterization date, history of diabetes, use of anti-hypertensive drugs including diuretics,  $\text{Ca}^{2+}$  channel blockers, renin-angiotensin system blockers,  $\alpha$ - and  $\beta$ -receptor blockers, combined use of statins, and active vitamin  $\text{D}_3$ . Meanwhile, blood samples were obtained after an overnight fast. Whole-blood hemoglobin (Hb), serum creatinine, urea nitrogen, albumin, prealbumin, serum phosphorus, and PTH were assayed by standard methods at the local laboratories. Echocardiography was assessed within 3 days after hospitalization.

Along with each echocardiographic examination, we also recorded the body mass index (BMI). Body surface area (BSA) was calculated according to the Stevenson formula in Chinese [8]. BMI and BSA were both recorded after drainage of the dialysate. Clinical BP was measured with a mercury sphygmomanometer after

at least 5 min of supine rest and averaged from 3 readings. Ultrafiltration, urine output, and total fluid removal were also included.

#### *Echocardiographic Examination*

All included patients received echocardiographic examination 4 times (Model GE Vivid E9) at 12-month intervals after drainage of the dialysate in our hospital. Images were taken of the parasternal view in patients lying in the left decubitus position. Left ventricular posterior wall thickness (LVPWT) and interventricular septal thickness (IVST) were evaluated by M-mode echocardiography and used to calculate LV mass using the Devereux formula [9]. LVH was defined as the LV mass/height<sup>2.7</sup> (LV mass divided by height in meters to the powers of 2.7) >52 g/m<sup>2.7</sup> in men and >47 g/m<sup>2.7</sup> in women as suggested by the 2013 ESH/ESC guidelines [10]. LV systolic function was assessed by ejection fraction (EF) measurement, and systolic dysfunction was defined as an EF <50%. The maximum velocity of the early (E) and late (A) phase of ventricular filling as well as the E/A ratio were calculated. The peak velocity of the early diastolic wave (e') was measured by pulse-wave tissue Doppler, with the sample volume close to the mitral valve annulus in the apical 4-chamber view in the lateral wall. We calculated the E/e' ratio. E/A ≤1, e' <10 cm/s, or E/e' >13 suggested the presence of left ventricular diastolic dysfunction (LVDD) according to the recommendation of the American Society of Echocardiography [11]. Left atrial diameter (LAD) and left atrial diameter index (LADI, LAD/BSA) were also evaluated. All echocardiographic measurements were performed by experienced echocardiographic technicians who were blinded to the clinical conditions.

#### *Statistical Analysis*

Data were expressed as mean ± standard deviation or median (interquartile range) based on the distribution type. Continuous measurements with a skewed distribution were normalized by logarithmic transformation and represented by median (interquartile range). The statistical analysis was performed using SPSS 22.0 (IBM SPSS, Somers, NY, USA). One-factor repeated-measures ANOVA was performed to estimate the changes in LV structural and functional indices (LV mass/height<sup>2.7</sup>, IVST, LVPWT, EF, LAD, LADI, E/A, E/e', and e') as well as BP, dialysis parameters, BMI, and biochemical data. A *p* value <0.05 (two-tailed) was considered statistically significant.

## **Results**

The baseline characteristics of the study subjects are shown in Table 1. A total of 40 patients were included. The underlying causes of end-stage renal disease (ESRD) were glomerulonephritis in 47.5%, hypertensive nephrosclerosis in 20%, diabetic nephropathy in 15%, polycystic kidney in 12.5%, and not identified in 5% of patients. Overall, 100% of the patients were using erythropoietin, 80.0% were receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers during the follow-up period, and 52.5% were using β-receptor blockers (Table 1).

One-factor repeated-measures ANOVA was performed to analyze the differences and trends in various clinical data. Data on LV structure and function status showed no significant difference in LV mass/height<sup>2.7</sup> (*p* = 0.580), IVST (*p* = 0.193), LVPWT (*p* = 0.216), or EF (*p* = 0.270) during the follow-up period. The differences in E/A ratio (*p* = 0.004), E/e' ratio (*p* = 0.006), and e' (*p* < 0.001) were statistically significant. Our data showed significant differences in LAD (*p* = 0.008), but the changes in LADI did not reach statistical significance (*p* = 0.090). Stable indices also included systolic blood pressure (SBP) (*p* = 0.259), diastolic blood pressure (DBP) (*p* = 0.442), and ultrafiltration (*p* = 0.321). There were differences in total fluid removal (*p* < 0.001), urine output (*p* < 0.001), BMI (*p* < 0.001), Hb (*p* < 0.001), albumin (*p* = 0.028), prealbumin (*p* = 0.001), ln(PTH) (*p* < 0.001), and serum phosphorus (*p* = 0.045) over time on PD treatment. In addition, our data showed that the rates of LVH at 0, 12, 24, and 36 months were 75.0, 67.5, 67.5, and 70.0%, respectively. The LV systolic dysfunction (EF <50%) rates were 2.5, 7.5, 5, and 7.5%, respectively. With respect to diastolic dysfunction, the rates of E/A ≤1 were 75, 82.5, 82.5, and 97.5%, and those of E/e' >13 were 52.5, 77.5, 82.5,

**Table 1.** Baseline characteristics of the study subjects

Characteristic	Value
Age, years	59.5 (47–68)
Male gender	23 (57.5%)
Diabetes	11 (27.5%)
Cause of ESRD	
Glomerulonephritis	19 (47.5%)
Diabetic nephropathy	6 (15.0%)
Hypertensive nephrosclerosis	8 (20.0%)
Polycystic kidney	5 (12.5%)
Unknown	2 (5.0%)
Medication use	
Diuretics	25 (62.5%)
RAAS blockers	32 (80.0%)
Ca <sup>2+</sup> channel blockers	23 (57.5%)
α-Receptor blockers	9 (22.5%)
β-Receptor blockers	21 (52.5%)
Erythropoietin	40 (100%)
Active vitamin D <sub>3</sub>	6 (15.0%)
Phosphorus binders	24 (60.0%)

Values are presented as median (interquartile range) or number of subjects (%). ESRD, end-stage renal disease; RAAS, renin-angiotensin-aldosterone system.

and 85.0%, respectively. The rates of  $e' < 10$  cm/s were 12.5, 17.5, 20.0, and 22.5%, respectively (Table 2). The trends of parameters over time are also shown in Figure 1.

According to our study, no significant differences were found in LV mass/height<sup>2.7</sup>, IVST, LVPWT, or EF during the follow-up period. In contrast, the E/A ratio and  $e'$  were decreased, and the E/ $e'$  ratio was increased. LAD was increased but LADI showed no significant changes. There were no significant progressions in LVH or systolic dysfunction throughout the 3-year observation. However, the incidence of LVDD increased progressively. These findings suggest that LV structure and systolic function may remain stable while diastolic function declines over time in long-term PD patients.

## Discussion

Previous studies have reported that cardiac structure and function changes started in the early stages of CKD and aggravated in patients with deteriorated renal function approaching or on dialysis [12, 13]. In this study, we found nonparallel progressions of cardiac structure and function in long-term PD patients. To our knowledge, this is the first study to analyze the dynamic changes of LV structure as well as LV diastolic and systolic function in PD patients with a long-term follow-up of PD.

LV mass tends to increase in ESRD patients prior to dialysis for a variety of reasons, including hypertension, other adverse loading conditions, and anemia. However, with regular dialysis, these pathologic conditions can be improved accordingly. Thus, no significant change in LV mass in continuous ambulatory PD over time is an acceptable outcome. We presumed that well-controlled BP was one reason why our long-term PD patients retained stable LV structure and cardiac systolic function. BP is undoubtedly a major determinant of LVH in CKD. Huting and Alpert [14] demonstrated that hypertension and hypercirculation contributed to

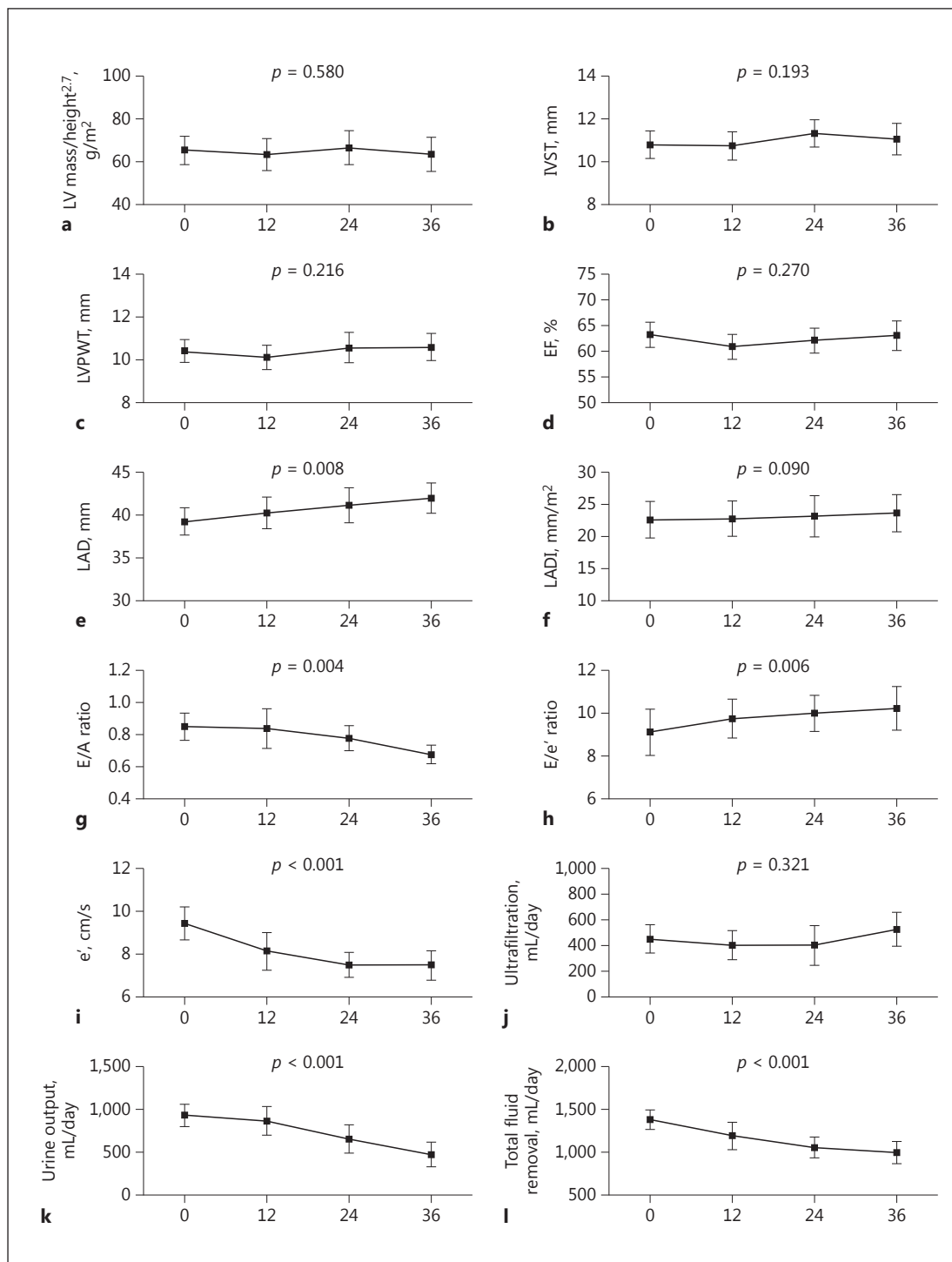
**Table 2.** Comparison of clinical parameters over time of patients on maintenance peritoneal dialysis

Characteristic	0 month	12 months	24 months	36 months	p value
LV mass/height <sup>2.7</sup> , g/m <sup>2.7</sup>	65.4±20.4	63.3±23.5	66.5±24.5	63.4±24.5	0.580
IVST, mm	10.8±2.0	10.8±2.1	11.3±2.0	11.1±2.3	0.193
LVPWT, mm	10.4±1.6	10.1±1.7	10.6±2.2	10.6±2.0	0.216
Ejection fraction, %	63.3±7.6	61.0±7.5	62.2±7.6	63.1±8.9	0.270
LAD, mm	39.3±5.1	40.2±5.7	41.1±6.3	42.0±5.5	0.008
LADI, mm/m <sup>2</sup>	22.6±2.8	22.8±2.7	23.2±3.2	23.7±2.9	0.090
E/A ratio	0.85±0.26	0.84±0.39	0.78±0.24	0.68±0.18	0.004
E/e' ratio	9.14±3.35	9.76±2.84	10.01±2.65	10.23±3.21	0.006
e', cm/s	9.42±2.37	8.15±2.74	7.50±1.83	7.47±2.19	<0.001
Body mass index	22.7±3.3	23.5±3.7	23.7±3.1	24.0±3.0	<0.001
SBP, mm Hg	143.2±20.0	147.6±21.2	144.3±21.6	139.7±18.3	0.259
DBP, mm Hg	87.4±14.4	88.1±14.1	86.4±13.3	84.9±10.3	0.442
Ultrafiltration, mL/day	449±337	401±300	401±480	524±410	0.321
Urine output, mL/day	934±394	868±530	657±519	478±464	<0.001
Total fluid removal, mL/day	1,383±355	1,198±496	1,058±376	996±399	<0.001
Hemoglobin, g/L	84.6±20.4	106.7±19.7	104.4±19.9	105.7±20.2	<0.001
Albumin, g/L	34.8±5.0	32.7±4.9	32.7±5.0	33.7±5.1	0.028
Prealbumin, g/L	0.31±0.07	0.29±0.10	0.26±0.08	0.26±0.07	0.001
Phosphorus, mmol/L	1.58±0.46	1.72±0.56	1.77±0.40	1.79±0.60	0.045
ln(PTH), pg/dl	5.4±0.9	4.6±1.0	4.9±1.0	5.2±1.1	<0.001
LVH	30 (75.0%)	27 (67.5%)	27 (67.5%)	28 (70.0%)	–
Ejection fraction <50%	1 (2.5%)	3 (7.5%)	2 (5.0%)	3 (7.5%)	–
E/A ≤1	30 (75.0%)	33 (82.5%)	33 (82.5%)	39 (97.5%)	–
E/e' >13	5 (12.5%)	7 (17.5%)	8 (20.0%)	9 (22.5%)	–
e' <10 cm/s	21 (52.5%)	31 (77.5%)	33 (82.5%)	34 (85.0%)	–

Values are presented as mean (standard deviation) or number of subjects (%). DBP, diastolic blood pressure; IVST, interventricular septal thickness; LAD, left atrial diameter; LADI, left atrial diameter index; LV, left ventricular; LVH, left ventricular hypertrophy; LVPWT, left ventricular posterior wall thickness; PTH, parathyroid hormone; SBP, systolic blood pressure.

the progression of LVH. Hypertension increases peripheral resistance and pressure load and promotes myocardial hypertrophy and myocardial fibrosis, leading to an increase in heart LV weight. The International Society for Peritoneal Dialysis recommends PD patients to maintain an SBP <140 mm Hg and a DBP <90 mm Hg [15]. However, it has been reported that the relationship between mortality and SBP in ESRD is a U-shaped curve [16]. A study reported that higher mortality was associated with lower BP and that lower BP may cause deterioration of cardiac structure and function [7]. In our 40 patients, the average value of SBP fluctuated from 139.7 to 147.6 mm Hg and DBP at values <90 mm Hg, indicating moderate BP control. As BP was stable during the whole follow-up, it may be partially explained why patients' LV structures and cardiac systolic functions remained stable.

The second reason was that we ensured stable ultrafiltration and adequate total fluid removal in our PD patients. Our PD center attaches great importance to urine volume and ultrafiltration to achieve euvolemia as far as possible. Our data indicated that although the patients' urine volumes decreased gradually, their ultrafiltration volumes remained stable. Ultrafiltration in PD patients could be affected by peritoneal function, nutritional status, dialysis method, and other factors, and no numerical target for ultrafiltration has been recommended. Several prospective observational studies revealed that ultrafiltration was an important predictor of PD survival [17, 18], and baseline ultrafiltration <750 mL/day was



**Fig. 1.** Longitudinal changes in values of left ventricular (LV) structure and functional indices as well as fluid status. Vertical lines denote 95% confidential interval and the x axis shows the time points (0, 12, 24, and 36 months). **a** LV mass/height<sup>2.7</sup>. **b** Interventricular septal thickness (IVST). **c** Left ventricular posterior wall thickness (LVPWT). **d** Ejection fraction (EF). **e** Left atrial diameter (LAD). **f** Left atrial diameter index (LADI). **g** E/A ratio. **h** E/e' ratio. **i** e' value. **j** Twenty-four-hour ultrafiltration volume. **k** Twenty-four-hour urine output. **l** Twenty-four-hour total fluid removal.



associated with poorer survival in anuric patients on automated peritoneal dialysis [17]. In the present study, a majority (75%) of patients were not anuric, and the ultrafiltration volume was stable during the whole follow-up. Although patients' urine output gradually decreased, we maintained the total fluid removal at  $\geq 1,000$  mL/day. We considered that stable ultrafiltration and adequate total fluid removal in these 40 patients were crucial for maintaining fluid balance, which may have delayed the progress of LV remodeling and dysfunction.

In contrast to the stable LV structure and cardiac systolic function, a high incidence of diastolic dysfunction was found in these 40 patients, and the E/A ratio, the E/e' ratio, and the e' values all showed a gradual decline. These results suggest that diastolic dysfunction got worse over time. It is being increasingly recognized that many patients with heart failure have preserved EF, and it was reported that diastolic heart failure was more frequent than systolic cardiac failure in patients with CKD [19]. Kunz et al. [20] showed that diastolic function deteriorated as the CKD progressed. Our findings are consistent with these studies. Previous studies reported that age, hypertension, systemic inflammation, and increased visceral fat were risk factors for LVDD in patients undergoing PD [21, 22]. Moreover, 1 study demonstrated that CKD-related anemia, hyperphosphatemia, hyperparathyroidism, and oxidative stress decreased LV compliance, which was a central pathophysiological feature of LVDD [23]. In this study, we found that the serum phosphorus levels increased (1.58, 1.72, 1.77, and 1.79 mmol/L at 0, 12, 24, and 36 months,  $p = 0.045$ ). It is well accepted that serum phosphorus is closely linked to vascular calcification and arterial stiffness [24]. Hyperphosphatemia may decrease vascular and myocardial compliance, which in turn may impair LV diastolic function. Our data also showed that anemia was not properly controlled. Traditionally, the Hb levels should be kept between 110 and 120 g/L in ESRD patients. However, the mean Hb levels in our 40 patients remained  $<110$  g/L. Anemia could accelerate heart rate and increase stroke volume, then gradually increase cardiac preload. Similarly, anemia may decrease myocardial compliance, affect ventricular filling, and worsen LV diastolic function [25]. These may have been the main mechanisms for progression of LV diastolic function in our study patients. Additionally, LAD may accurately reflect the LV diastolic function in dialysis patients [26]. In this study, LAD and LADI were both increased, although the latter did not reach statistical significance. This phenomenon may have been caused by the relatively small number of subjects. Besides, the changes in LADI may show a significant difference with increasing length of follow-up. Our data also suggest that LV diastolic function may deteriorate over time in PD patients.

Our study has its strengths. First, we collected complete echocardiography data (4 times) to investigate the changes in LV structure and function in PD patients. In addition, we simultaneously analyzed the changes in related clinical indices. The limitations include the fact that this was a single-center observational study with a small sample size. Moreover, we only employed resting echocardiography rather than combining data with stress echocardiography, so we did not assess cardiac functional reserve. Multicenter studies with a large sample size and prospective studies are needed to verify our results.

In summary, this study demonstrated the dynamic changes in LV structure and function over time in PD patients. We found that long-term PD patients had stable LV structure and systolic function, while diastolic function decreased over time.

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### Statement of Ethics

This study was approved by the hospital's ethics committee.

### Disclosure Statement

The authors certify that none of them has any financial or other conflict of interest in connection with this paper.

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