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ORIGINAL PAPER

# Left atrial strain associated with alterations in cardiac diastolic function in patients with end-stage renal disease

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**Abstract**
The purpose of this study was to investigate the correlation between left atrial (LA) strain and alterations in cardiac diastolic function in patients with end-stage renal disease. 59 patients with stage 5 chronic kidney disease (CKD5) and 30 healthy controls were enrolled in this study. Patients with CKD5 were divided into three groups, from normal to Grade II diastolic dysfunction. LA longitudinal strain was evaluated using two-dimensional speckle tracking echocardiography. The peak LA longitudinal strain values (PALS) and LA stiffness index were recorded as the main parameters. Comparing with control group, index of LA volume (LAVI, $14.57 \pm 6.92$ vs. $20.15 \pm 6.21$ vs. $30.49 \pm 10.66$ vs. $42.99 \pm 18.77$) and index of left ventricular mass (LVMI, $77.64 \pm 12.60$ vs. $103.83 \pm 15.90$ vs. $155.01 \pm 36.92$ vs. $178.34 \pm 44.47$) significantly increased in CKD5 patients, along with the decline of diastolic function ($p < 0.001$). An incremental reduction in PALS ($51.75 \pm 5.82$ vs. $40.23 \pm 12.72$ vs. $36.37 \pm 8.59$ vs. $33.33 \pm 9.30$, $p < 0.001$) as well as increase in LA stiffness index ($0.11 \pm 0.02$ vs. $0.25 \pm 0.10$ vs. $0.38 \pm 0.21$ vs. $0.61 \pm 0.51$, $p = 0.003$) in apical 4 chamber (A4C) view and global value were observed in CKD5 patients, and higher LA stiffness index were shown in patients with Grade II diastolic dysfunction. What's more, estimated glomerular filtration rate was independently correlated with PALS–A4C (B = 0.084, 95% CI 0.002–0.166, $p = 0.046$), and LAVI adversely correlated with PALS–A4C (B = − 0.191, 95% CI − 0.379 to − 0.002), $p = 0.047$) and correlated with LA stiffness index in A4C (B = 0.011, 95% CI 0.006 –0.017, $p < 0.001$). In conclusion, LA longitudinal strain, combined with LAVI and LVMI, were independently associated with the decline in diastolic function in CKD5 patients, which might provide novel cardiovascular events predictors in these patients.

**Keywords** Left atrial strain · Diastolic function · Chronic kidney disease · Speckle tracking imaging

## Introduction

Patients with chronic kidney disease (CKD) experience severe reductions in life quality and life expectancy, which are particularly driven by the increasing risk of cardiovascular (CV) diseases, the leading causes of high mortality [1–3]. Cardiac structural and functional changes, including declined cardiac diastolic function, are the most prevalent CV risks in CKD patients developing end-stage renal disease (ESRD) [4–7]. Diastolic dysfunction could be diagnosed clinically once the clinical symptoms and signs of heart failure (HF) were found. However, in patients with normal or slightly decreased left ventricular ejection fraction (LVEF), it is difficult to diagnose left ventricular (LV) diastolic dysfunction, due to the lack of simple and reliable diagnostic criteria.

The gold standard of diastolic function evaluation was supposed to be obtained invasively by cardiac catheterization. Nevertheless, noninvasive echocardiographic evaluation of LV diastolic function plays an important role in clinical practice. According to a recent guideline from the American Society of Echocardiography, an algorithm for diagnosis of LV diastolic dysfunction was recommended, including multiple parameters such as tissue Doppler imaging (TDI) of mitral annulus velocity, the left atrium volume

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index (LAVI), Doppler mitral flow velocities, etc. [8]. Although the standard of LV diastolic dysfunction has been widely used in clinic, it remains complicated in acquisition and interpretation. In addition, the spectrum of diastolic index varied among individuals, which sometimes might not meet the strict definition of any type of LV diastolic dysfunction, making the interpretation challenging [9, 10].

Left atrial (LA) strain, using two-dimensional (2D) speckle tracking, is angle-independent and less susceptible to the limitations of Doppler echocardiography. It has been used for the assessment of LA function and the categorization of LV diastolic dysfunction in patients with hypertension, diabetes, hypertrophic cardiomyopathy and diastolic HF [11–14]. However, there are few studies investigating the relationship between the LA strain and LV diastolic function in patients with stage 5 CKD (CKD5). To this end, our objective for this study was to investigate whether LA strain is associated with alterations in cardiac diastolic function in CKD5 patients, which might provide novel CV events predictors in this population.

## Methods

### Study population

A total of 59 patients with CKD5 waiting for renal transplantation at random were enrolled from the inpatient or outpatient department of the First Affiliated Hospital of Sun Yat-sen University (SYSU) from August 2017 to August 2018. This study complied with the Declaration of Helsinki, and the protocol was approved by the Ethic Committee of SYSU. Written consent was obtained from all enrolled patients.

Inclusion criteria were as follows: ESRD waiting for kidney transplantation; age ≥ 18 years, renal dialysis for at least 3 months, LVEF > 50%, normal sinus rhythm, without symptoms of CV disease. Exclusion criteria included age < 18 years, combined with systemic or organic diseases (except diabetes mellitus), clinical conditions that may limit study participation (e.g., respiratory distress and infections), decreased LV systolic function (LVEF < 50%), echocardiography images might interfere accurate strain measurements: poor quality, image loops did not display all LA segments, failure in speckle tracking of atrial boundaries, or lack of recognizable R-R interval.

Thirty healthy subjects, without any known disease, of well-matched age and gender, were recruited as the control group.

### Clinical and laboratory evaluation

Demographic parameters (age, gender, height and weight) and clinical variables including blood pressure and combined diseases were collected. The formula for calculating body surface area (BSA) was $(0.0061 \times height + 0.0124 \times weight - 0.0099)$ [15]. Body mass index (BMI) was calculated as weight (kg) divided by squared height ($m^2$). Venous blood samples were collected in the morning after an overnight fasting. Serum NT-pro BNP, urea, creatinine and uric acid were detected. The estimated glomerular filtration rate (eGFR) was calculated using the abbreviated MDRD formula: eGFR (ml/min/1.73 $m^2$) = $175 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ for women}) \times (1.212 \text{ for black patients})$ [16].

### Echocardiography

All the patients were imaged in left lateral decubitus or supine position during smooth respiration, using a commercially available echocardiography system (Philip EPIQ7C, Andover, Massachusetts, USA) with a 1.7–3.4 MHz phased-array transducer. Electrocardiogram was simultaneously recorded in all cases. Echocardiographic evaluation was conducted according to current guideline and recommendations [17]. All echocardiographic variables were measured three times and then averaged.

### M-mode and conventional 2-dimensional (2D) echocardiography

The diameter of LV at the end of systole and diastole (LVEDd, LVESd), interventricular septum thickness (IVSd), posterior wall thickness (LVPWd) were measured by M-mode echocardiography in parasternal long-axis view. LV mass (LVM) was calculated from the parasternal long-axis view using the following formula: $\text{LVM} = 0.8 \times [1.04 (\text{LVEDd} + \text{IVSd} + \text{LVPWd})^3 - (\text{LVEDd})^3] + 0.6$. The LVM index (LVMI) was equal to LVM divided by BSA. LVEF was measured by biplane Simpson method in the apical four chamber (A4C) and apical two chamber (A2C) view. LVM was calculated with a validated method and indexed for BSA. LA volume (LAV) was measured using the disk summation algorithm, similar to that used in LV volume, and the LA endocardial borders were traced in both the A4C and A2C views. The LA volume index (LAVI) was equal to LAV divided by BSA.

### Pulsed wave Doppler (PW) and pulsed wave tissue Doppler imaging (PW-TDI)

PW examination of the mitral inflow was performed to measure the early (E) and late diastolic peak velocity (A), with their ratio (E/A) calculated. PW-TDI was performed in the A4C view at a frame rate over 100 frames/s. The tissue Doppler sample volume was placed at septal and lateral sides of mitral annulus, and the motion curve of mitral valve

annulus was recorded over five cardiac cycles, while the average values were calculated. Then we measured the septal and lateral mitral valve annular peak systolic velocity ($S'_{septal}$ and $S'_{lateral}$), early diastolic velocity ($E'_{septal}$ and $E'_{lateral}$) and late diastolic velocity ($A'_{septal}$ and $A'_{lateral}$). The peak systolic and diastolic velocity (S′, E′ and A′) was the average value of the septal and lateral mitral valve annular. The ratio ($E/E'_{septal}$ and $E/E'_{lateral}$) was also calculated, and the average value (E/E′) was used.

### LV diastolic function

The assessment of LV diastolic function was according to the current recommendations [8]. There were four recommended variables for evaluating LV diastolic function, and their abnormal cutoff values were annular E′ velocity (septal E′ < 7 cm/s, lateral E′ < 10 cm/s), average E/E′ ratio > 14, LA maximum volume index > 34 mL/m$^2$, and peak TR velocity > 2.8 m/s. LV diastolic function is normal if more than half of the available variables do not meet the cutoff values for identifying abnormal function. Then, the key variables recommended for assessment of LV diastolic function grade include mitral flow velocities, mitral annular e′ velocity, E/e′ ratio, peak velocity of TR jet, and LA maximum volume index. When two of the three or all three variables (E/E′ ratio, peak velocity of TR jet, and LA maximum volume index) met the cut-off threshold, the average LA pressure (LAP) was elevated, with Grade II diastolic dysfunction. Conversely, if two of the three or all three variables did not meet the cut-off threshold, LAP was normal and Grade I diastolic dysfunction was present. According to this standard, the patients with CKD5 were divided into three groups. Group A enrolled patients with normal LAP and normal LV diastolic function, Group B included patients with Grade I diastolic dysfunction, and Group C included patients with Grade II diastolic dysfunction. We did not recruit Grade III patients into this study due to the potential symptoms of HF in these patients.

### Left atrial strain

After acquiring three consecutive cardiac cycles imaging in A4C and A2C views at a frame rate of 50–60 frames/s, we used the 2D speckle tracking software (Philip Qlab 10.0, Andover, Massachusetts, USA) to delineate the LA endocardial border, taking care to exclude the appendage and pulmonary veins from the LA cavity. Then, a composite LA longitudinal strain curve throughout the cardiac cycle was generated according to the 2018 consensus document [18]. This curve comprised six individual atrial segments and the white dot curve stood for the global strain. If more than one atrial segment had to be excluded from analysis due to suboptimal visualization and tracking, an alternative loop was supposed to be selected to ensure the completion of analysis for each subject. The peak LA longitudinal strain values (PALS) in apical 4 and 2 chamber views (PALS–A4C, PALS–A2C) were derived from the maximal inflection point on the corresponding composite LA strain curve among the diastolic phase, and the global PALS was the average of the PALS in A4C and A2C views. LA stiffness index was estimated by the ratio of E/E′ and PALS [19]. According to the 2018 consensus document, the apical long-axis view was difficult for LA strain analysis, so this view did not be taken into consideration.

### Measurement variability

To assess reproducibility, these measurements were repeated by the same observer on the same echocardiographic images in 15 patients at least 1 weeks apart. These parameters of LA strain were also analyzed by another independent observer to determine interobserver variability.

### Statistical analysis

Statistical analyses were performed using SPSS 16.0 (SPSS, Inc., Chicago, IL, USA). All continuous variables were expressed as mean ± standard deviations (SDs), and categorical variables are presented as frequencies and percentages. Chi-square test was used to compare categorical variables, One way ANOVA for continuous parameter variables, and Kruskal–Wallis for continuous non-parameter variables. Univariate and multivariate linear regression analyses on LA strain and LA stiffness index were performed to identify the correlation between clinical and echocardiographic variables with the LA strain parameters. The factors related at the $p < 0.10$ level were selected as independent variables for multivariate analysis, and $p < 0.05$ was considered significant.

## Results

### Clinical characteristics

Clinical data in this study was detailed in Table 1. The mean value of systolic and diastolic blood pressure, serum NT-pro BNP, urea and creatinine were significantly higher in patients with CKD5 than control group ($p < 0.05$), with lower eGFR level. However, there were no differences in age, gender distribution, BMI, BSA and uric acid between patients with CKD5 and control group ($p > 0.05$).

**Table 1** Comparison of clinical characteristics among the CKD5 patient groups and control group

| | Control group (n = 30) | Patient group | | | *p* value |
|---|---|---|---|---|---|
| | | Group A (n = 16) | Group B (n = 23) | Group C (n = 20) | |
| LV diastolic dysfunction grade | Normal | Normal | Grade I | Grade II | |
| Age (years) | 40.55 ± 11.40 | 36.36 ± 9.90 | 46.67 ± 12.67 | 44.41 ± 16.28 | 0.170 |
| Male sex (n, %) | 13 (45.0) | 7 (43.7) | 13 (56.0) | 8 (40.0) | 0.722 |
| BMI (kg/m$^2$) | 22.68 ± 2.26 | 21.66 ± 3.06 | 22.31 ± 3.30 | 21.72 ± 2.89 | 0.794 |
| BSA (m$^2$) | 1.64 ± 0.22 | 1.69 ± 0.17 | 1.63 ± 0.16 | 1.60 ± 0.17 | 0.567 |
| Hypertension (n, %) | 0 (0.0) | 12 (75.0) | 19 (82.6) | 17 (85.0) | 0.732 |
| Diabetes (n, %) | 0 (0.0) | 2 (12.5) | 4 (17.3) | 3 (15.0) | 0.916 |
| Systolic BP (mmHg) | 121.45 ± 5.92 | 141.82 ± 18.60* | 151.96 ± 16.56* | 160.62 ± 14.55*$^{\#}$ | < 0.001 |
| Diastolic BP (mmHg) | 76.63 ± 4.84 | 92.09 ± 12.33* | 89.50 ± 12.39* | 90.56 ± 14.08* | 0.010 |
| NT-pro BNP (pg/mL) | 52.50 ± 15.22 | 770.60 ± 1059.75 | 9923.95 ± 14,938.83 | 31,055.25 ± 48,666.65*$^{\#\S}$ | 0.029 |
| Urea (mmol/L) | 4.82 ± 1.28 | 27.51 ± 14.35* | 18.98 ± 8.23*$^{\#}$ | 21.02 ± 7.09* | < 0.001 |
| Creatinine (umol/L) | 68.55 ± 20.06 | 946.70 ± 267.95* | 783.33 ± 388.28* | 938.00 ± 341.25* | < 0.001 |
| Uric acid (umol/L) | 346.87 ± 95.03 | 480.50 ± 139.86* | 358.33 ± 144.78 | 368.06 ± 82.52 | 0.057 |
| Dialysis duration (months) | 0 | 11.91 ± 24.02 | 11.12 ± 19.23 | 23.25 ± 23.02 | 0.142 |
| eGFR (ml/min/1.73 m$^2$) | 112.00 ± 19.59 | 8.50 ± 2.72* | 8.91 ± 3.57* | 7.19 ± 2.58* | < 0.001 |

*$P < 0.05$ versus control group, $^{\#}P < 0.05$ versus Group A, $^{\S}P < 0.05$ versus Group B

## Routine echocardiographic analysis

Parameters derived from routine echocardiography were described in Table 2. Increasing tendency in the parameters of LA, LAVI, IVSd, LVEDd, LVESd, LVPWd and LVMI were observed in CKD5 patients, when compared with healthy individuals ($p < 0.001$). Meanwhile, LA, LAVI and LVMI significantly increased, along with the decline of diastolic function in patients with CKD5 ($p < 0.05$) in comparison with control group. However, there was no obvious difference between control group and Group A (CKD5 patients with normal LAP). What's more, increasing LVEDd, LVESd and LVPWd were also shown in diastolic dysfunction (Grades I and II) patients with CKD5 ($p < 0.05$). The early diastolic velocity (E) of mitral valve significantly increased in CKD5 patients with Grade II diastolic dysfunction when comparing with control group, Group A (with normal LAP) and Group B (Grade I diastolic dysfunction) ($p < 0.05$). Nevertheless, no significant differences were found among the latter three groups. The ratio of E/A, the septal and lateral mitral valve annular peak systolic velocity ($S'_{septal}$ and $S'_{lateral}$) and early diastolic velocity ($E'_{septal}$ and $E'_{lateral}$), and the average value of S and E varied between control group and CKD5 patients ($p < 0.05$), but the consistent reduction in these parameters with graded diastolic dysfunction severity was not observed in CKD5 patients.

There observed no significantly differences between control group and CKD5 patients in parameters of AO, LVEF, TR-Vmax and the late diastolic velocity of the septal and lateral mitral valve annular and the average valve ($A'_{septal}$, $A'_{lateral}$ and A).

## Left atrial strain measurement (Table 3)

An incremental reduction in PALS in A4C view and average value were shown in individuals with normal LAP, Grades I and II diastolic dysfunction, and lower PALS were observed in CKD5 patients, in comparison with the control group ($p < 0.05$).

Increasing LA stiffness index in A4C and A2C and the average value were exhibited in diastolic dysfunction patients with CKD5 when compared with control group ($p < 0.05$), and higher LA stiffness index were also shown in patients with Grade II diastolic dysfunction, when compared with CKD5 patients with normal LAP ($p < 0.05$). However, when we compare between Groups B and C, only the LA stiffness index in A4C and global value were higher in Grade II diastolic dysfunction patients with CKD5 (Group C, $p < 0.05$).

In order to investigate which clinical and echocardiographic variables were independently correlated with PALS and LA stiffness index in A4C, multiple regression analysis were performed (Table 4). It showed that eGFR was independently correlated with PALS–A4C (B = 0.084, $p = 0.046$), and LAVI were the independently correlated with PALS–A4C (B = − 0.191, $p = 0.047$) and LA stiffness index in A4C (B = 0.011, $p < 0.001$).

**Table 2** Comparison of routine echocardiographic parameters among the CKD5 patient groups and control group

| | Control group (n = 30) | Patient groups | | | *p* value |
|---|---|---|---|---|---|
| | | Group A (n = 16) | Group B (n = 23) | Group C (n = 20) | |
| LV diastolic dysfunction grade | Normal | Normal | Grade I | Grade II | |
| AO (mm) | 30.72 ± 4.82 | 34.45 ± 4.25 | 34.58 ± 5.46 | 33.37 ± 3.89 | 0.159 |
| LA (mm) | 28.81 ± 3.22 | 31.00 ± 3.61 | 37.17 ± 3.38*# | 42.87 ± 3.89*#§ | < 0.001 |
| LAVI (ml/m$^2$) | 14.57 ± 6.92 | 20.15 ± 6.21 | 30.49 ± 10.66*# | 42.99 ± 18.77*#§ | < 0.001 |
| IVSd (mm) | 8.81 ± 1.07 | 10.81 ± 1.08* | 12.50 ± 1.44* | 12.76 ± 1.61* | < 0.001 |
| LVEDd (mm) | 44.91 ± 3.38 | 48.00 ± 4.09 | 53.79 ± 5.76*# | 56.31 ± 6.41*# | < 0.001 |
| LVESd (mm) | 26.81 ± 2.82 | 30.63 ± 3.01 | 34.62 ± 5.88*# | 37.00 ± 6.23*# | < 0.001 |
| LVPWd (mm) | 8.27 ± 1.27 | 9.27 ± 0.90 | 10.21 ± 1.10*# | 10.75 ± 1.42*# | < 0.001 |
| LVMI (g/m$^2$) | 77.64 ± 12.60 | 103.83 ± 15.90 | 155.01 ± 36.92*# | 178.34 ± 44.47*#§ | < 0.001 |
| LVEF (%) | 70.54 ± 4.96 | 64.36 ± 4.61 | 64.92 ± 7.84 | 63.00 ± 9.34 | 0.074 |
| TR-Vmax (m/s) | 2.07 ± 0.26 | 2.30 ± 0.32 | 2.23 ± 0.29 | 2.42 ± 0.48 | 0.404 |
| E (cm/s) | 73.91 ± 13.13 | 71.78 ± 22.67 | 75.79 ± 22.78 | 102.76 ± 24.22*#§ | < 0.001 |
| A (cm/s) | 54.91 ± 9.41 | 69.25 ± 13.12* | 88.79 ± 18.18*# | 113.59 ± 27.20*#§ | < 0.001 |
| E/A | 1.38 ± 0.34 | 1.04 ± 0.28* | 0.87 ± 0.26* | 0.96 ± 0.34* | < 0.001 |
| S′ (cm/s) | 10.15 ± 2.09 | 8.24 ± 1.43* | 7.80 ± 1.44* | 7.80 ± 1.75* | 0.001 |
| $S'_{septal}$ | 9.87 ± 1.95 | 7.54 ± 1.25* | 7.50 ± 1.75* | 7.73 ± 1.76* | < 0.001 |
| $S'_{lateral}$ | 10.41 ± 2.75 | 8.93 ± 1.72 | 8.11 ± 1.35* | 8.31 ± 2.26* | 0.010 |
| E' (cm/s) | 11.78 ± 3.03 | 7.69 ± 2.62* | 6.89 ± 1.85* | 7.42 ± 2.47* | < 0.001 |
| $E'_{septal}$ | 10.37 ± 2.69 | 6.39 ± 2.20* | 6.09 ± 1.51* | 6.09 ± 1.72* | < 0.001 |
| $E'_{lateral}$ | 13.20 ± 3.68 | 8.99 ± 3.41* | 7.69 ± 2.35* | 8.73 ± 3.42* | < 0.001 |
| A' (cm/s) | 10.21 ± 1.54 | 10.03 ± 1.71 | 9.83 ± 1.67 | 10.17 ± 1.65 | 0.648 |
| $A'_{septal}$ | 9.50 ± 1.75 | 9.01 ± 1.52 | 9.26 ± 1.57 | 9.57 ± 2.05 | 0.687 |
| $A'_{lateral}$ | 10.94 ± 1.59 | 11.04 ± 2.58 | 10.39 ± 2.39 | 10.76 ± 2.29 | 0.788 |
| E'/A' | 1.19 ± 0.41 | 0.78 ± 0.26* | 0.73 ± 0.22* | 0.72 ± 0.21* | < 0.001 |
| $E'/A'_{septal}$ | 1.14 ± 0.42 | 0.72 ± 0.27* | 0.67 ± 0.18* | 0.65 ± 0.14* | < 0.001 |
| $E'/A'_{lateral}$ | 1.24 ± 0.47 | 0.83 ± 0.30* | 0.78 ± 0.29* | 0.83 ± 0.31* | 0.001 |
| E/E' | 6.83 ± 2.04 | 11.95 ± 4.29* | 12.97 ± 4.71* | 12.94 ± 5.65* | 0.001 |
| $E/E'_{septal}$ | 7.53 ± 1.88 | 12.59 ± 4.60* | 14.19 ± 4.67* | 14.84 ± 6.91* | 0.001 |
| $E/E'_{lateral}$ | 6.13 ± 2.32 | 10.13 ± 4.39* | 11.75 ± 5.13* | 10.82 ± 5.17* | 0.008 |

*AO* aortic root, *LA* left atrial, *LAVI* the index of LA volume, *IVSd* diameter of inter ventricular septum, *LVEDd* LV diameter at the end of diastolic phase, *LVESd* LV diameter at the end of systolic phase, *LVPWd* diameter of LV post wall, *LVMI* the index of LV mass, *TR-Vmax* the maximum velocity of Tricuspid valve regurgitation

*$P < 0.05$ versus control group, #$P < 0.05$ versus Group A, §$P < 0.05$ versus Group B

**Table 3** Comparison of LA strain measurements among the CKD5 patient groups and control group

| | Control group (n = 30) | Patient group | | | *p* value |
|---|---|---|---|---|---|
| | | Group A (n = 16) | Group B (n = 23) | Group C (n = 20) | |
| LV diastolic dysfunction grade | Normal | Normal | Grade I | Grade II | |
| PALS–A4C | 51.75 ± 5.82 | 40.23 ± 12.72* | 36.37 ± 8.59* | 33.33 ± 9.30* | < 0.001 |
| LA stiffness index in A4C | 0.11 ± 0.02 | 0.25 ± 0.10 | 0.38 ± 0.21* | 0.61 ± 0.51*#§ | 0.003 |
| PALS–A2C | 48.90 ± 8.35 | 36.11 ± 11.82* | 38.75 ± 10.12* | 35.41 ± 12.36* | 0.039 |
| LA stiffness index in A2C | 0.12 ± 0.04 | 0.27 ± 0.11 | 0.35 ± 0.16* | 0.59 ± 0.45*# | 0.001 |
| PALS-GLOBAL | 48.18 ± 7.51 | 37.94 ± 9.61* | 37.51 ± 8.86* | 32.06 ± 10.16* | 0.002 |
| LA stiffness index-GLOBAL | 0.12 ± 0.05 | 0.22 ± 0.06 | 0.35 ± 0.10* | 0.67 ± 0.48*#§ | < 0.001 |

*PALS* peak LA longitudinal strain values, *A4C* apical 4 chamber view, *A2C* apical 2 chamber view

*$P < 0.05$ versus control group, #$P < 0.05$ versus Group A, §$P < 0.05$ versus Group B

**Table 4** Predictors of transformed PALS–A4C and LA stiffness index in A4C by univariate and multivariate linear regression analysis

| | Univariate | | Multivariate | | | |
|---|---|---|---|---|---|---|
| | β | *p* | B (95% CI) | *p* | Model R2 | Model *P* |
| PALS–A4C | | | | | 0.205 | 0.004 |
| SBP | – 0.415 | 0.001 | | | | |
| DBP | – 0.246 | 0.065 | | | | |
| NT-pro BNP | – 0.171 | 0.272 | | | | |
| Urea | – 0.136 | 0.326 | | | | |
| Creatinine | – 0.096 | 0.488 | | | | |
| eGFR | 0.371 | 0.007 | 0.084 (0.002, 0.166) | 0.046 | | |
| LVMI | – 0.365 | 0.005 | | | | |
| LAVI | – 0.372 | 0.004 | – 0.191 (– 0.379, – 0.002) | 0.047 | | |
| E/A | 0.359 | 0.006 | | | | |
| E/E’ | – 0.314 | 0.017 | | | | |
| LA stiffness index in A4C | | | | | 0.252 | < 0.001 |
| SBP | 0.29 | 0.029 | | | | |
| DBP | 0.061 | 0.653 | | | | |
| NT-pro BNP | 0.179 | 0.25 | | | | |
| Urea | 0.027 | 0.848 | | | | |
| Creatinine | 0.107 | 0.439 | | | | |
| eGFR | – 0.266 | 0.056 | | | | |
| LVMI | 0.376 | 0.004 | | | | |
| LAVI | 0.513 | < 0.001 | 0.011 (0.006, 0.017) | < 0.001 | | |
| E/A | – 0.265 | 0.047 | | | | |
| E/E’ | 0.268 | 0.044 | | | | |

*PALS–A4C* peak LA longitudinal strain values in apical 4 chamber view, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *LVMI* LV mass index, *LAVI* LA volume index

### Observer variability

Intra-observer variability for PALS in A4C and A2C by inter-class correlation was 0.901 ($p = 0.001$) and 0.896 ($p = 0.003$), respectively. In terms of LA stiffness index, the inter-class correlation was 0.981 ($p < 0.001$) in A4C and 0.989 ($p < 0.001$) in A2C view. Inter-observer variability for PALS in A4C and A2C by inter-class correlation was 0.845 ($p = 0.002$) and 0.801 ($p = 0.005$), respectively. In terms of LA stiffness index, the inter-class correlation was 0.972 ($p < 0.001$) in A4C and 0.981 ($p < 0.001$) in A2C view.

## Discussion

The main findings of this study are as follows: (1) the PALS values in apical 4 decreased in CKD5 patients, while higher LA stiffness index in A4C view as well as LAVI and LVMI were shown with declined diastolic function. (2) The level of eGFR independently correlated with PALS. LAVI was adverse independently correlated with PALS, but had correlation with LA stiffness index. To the best of our knowledge, the present study is the first study to demonstrate the relationship between LA longitudinal strain and diastolic dysfunction in Chinese patients with CKD5.

In this study, systolic and diastolic BP, LVMI increased in patients with CKD5, and the LVMI increased with the decreased diastolic function, while LVEF remained normal. This finding was in line with previous studies which illustrated that subclinical diastolic dysfunction and LV hypertrophy (LVH) were the most common echocardiographic manifestation in asymptomatic CKD patients on hemodialysis [20]. Besides, our study added evidence that the inappropriate LV remodeling process was accompanied by progressive deterioration of diastolic function [21]. The most common conditions related to diastolic dysfunction are aging, hypertension, diabetes, LVH, coronary heart disease, and so on, all of which are common complications in CKD patients. These complications are usually associated with the development of myocardial fibrosis and decreased ventricular compliance, which are pathological markers of diastolic HF. Also, LVH is the principal myocardial alteration in patients with CKD [22].

Some studies showed that elevated E/E’ values were associated with LV end-diastolic pressure, but an increase

in a single parameter of E/E' in patients with preserved LVEF may not be entirely accurate [23, 24]. It was also found that E/E' could not differentiate the severity of diastolic dysfunction in CKD5 patients of in this study. However, increasing LAVI with decreased diastolic function in CKD5 patients were shown in this study, similar to that in previous studies [11]. It was reported that LA enlargement was independent of LVMI and diastolic dysfunction in the CKD5 patients. Furthermore, LAVI was an independent predictor of future adverse CV outcomes [25, 26].

By comparison, PALS in A4C value was significantly different between control group and patient groups in this study, and it had been shown that PALS in A4C incrementally reduced with decreased diastolic function in CKD5 patients, but there was no significantly differences among patient groups. It was not completely identical with the study of Amita's et al., which showed that peak LA strain values differed among all diastolic dysfunction grades [11]. Possible explanations might be the patients with CKD5 had the similar susceptible effects on the LA strain and diastolic function, such as age, hypertension, diabetes and RAAS system [27, 28]. PALS in A2C didn't show incremental reduction among patient groups in this study. Thus, in order to investigate which clinical and echocardiographic variables were independently correlated with LA strain, only the parameters of LA strain in A4C was considered.

Stiffness is defined as the force required to make the displacement of a passive spring per unit length. Physiologically, it is a change in the pressure required to increase the volume of a passive container. The ratio of invasively measured PCWP and LA systolic strain is used to estimate LA stiffness. Alternatively, the E/E' ratio can be used as a noninvasive measure instead of PCWP [29]. Studies showed that diastolic HF was associated with greater degree of LA stiffness [30]. It was in line with this study that LA stiffness index significantly increased in CKD5 patients with Grade II diastolic dysfunction. Also, eGFR and LAVI were independently correlated with PALS and LA stiffness index in A4C in this study. As a result, PALS and noninvasive LA stiffness index combined with LAVI might help recognize the degree of diastolic dysfunction, thus potentially provide novel predictors for CV events in CKD5 patients.

Nevertheless, there are a few limitations. On one hand, this is a single-center study, and the sample size of the study is moderate. Thus, these findings need to be verified in a larger population. On the other hand, decreased PALS and increased LA stiffness may be due to LA fibrosis, secondary to RAAS activation as a consequence of CKD and HT. We were unable to confirm an increase in atrial fibrosis in CKD patients by histopathology, which was beyond the scope of this study.

## Conclusion

To conclude, PALS was significantly decreased and noninvasive LA stiffness index increased in CKD5 patients. PALS and noninvasive LA stiffness index combined with LAVI and LVMI were independently associated with the declined diastolic function in CKD5 patients, which might provide potential CV events predictors.

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### Compliance with ethical standards

**Conflict of interest** The authors report no conflicts of interest in this work.

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