Estimation of Left Atrial Function Using Four-Dimensional Auto Left Atrial Quantify Echocardiography in Patients with End-Stage Renal Disease

li zhao[1], xuan su[1], Lini Xian[1], Jian Chen[1], Xiaolei Song[1], Qinghui Wang[1], and Yunchuan Ding[2]

[1]Yanan Hospital of Kunming City
[2] Yanan Hospital of Kunming City

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Abstract

Background: Cardiovascular impairment is an important complication of end-stage renal disease (ESRD) undergoing hemodialysis (HD) therapy. Left atrial (LA) deformation is closely related to left ventricular (LV) filling pressure and dysfunction, but quantification of LA dysfunction remains a challenge. The purpose of this study was to evaluate the LA function in ESRD patients using four-dimensional(4D) auto left atrial quantification(4D-LAQ). Methods: Thirty-seven ESRD patients (aged 51.68±15.98 years; 43% male) on HD and 34 healthy individuals (aged 42.03±11.50 years; 38% male) were enrolled in the study. All participants underwent conventional echocardiographic examinations and 4D-LAQ. The measurements of LA dimension, volume, emptying fraction, and longitudinal/circumferential strain parameters during triphasic were obtained from the LV long axis and apical 4-chamber views, which were taken offline using software (GE EchoPac 203). Results: In patients with ESRD, LA dimension and volume were higher than the healthy group, while the LASr (22.54±6.14 vs 33.74±5.07; $p<0.05$), LAScd (-12.54±5.83 vs -20.03±5.21;$p<0.05$), LASct (-10.00±4.93 vs -13.56±5.17;$p<0.05$), LASr-c (28.00±6.61 vs 35.29±7.24;$p<0.05$), and LAScd-c (-13.27±5.58 vs -18.47±8.65; $p<0.05$) were significantly lower. Furthermore, a good positive correlation was observed between the LAEF, LASr, and LAScd-c values and LV filling pressure, which reflect diastolic dysfunction. Conclusion: We demonstrated that the LA strain in dialysis patients was impaired before the occurrence of LA dilation. LA strain is more sensitive than traditional echocardiographic parameters, and LASr and LAScd-c may be useful to detect early myocardial involvement.

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[1] Department of Ultrasound, Yanan Hospital of Kunming City, the Affiliated Hospital of Kunming Medical University, Kunming, Yunnan Province, 650051, China

[2] Clinical Research Center of Cardiovascular Ultrasound, Yunnan Province, 650051, China

[3] Yunnan Province Key Laboratory of Cardiovascular Diseases, Kunming, Yunnan Province, 650051, China

*Address correspondence to:Qinghui Wang, Department of Ultrasound, Yanan Hospital of Kunming City, the Affiliated Hospital of Kunming Medical University, Kunming, Yunnan Province, 650051, China, E-mail: wqh962099@163.com.Yunchuan Ding, Department of Ultrasound, Yanan Hospital of Kunming City, the

Affiliated Hospital of Kunming Medical University, Kunming, Yunnan Province, 650051, China, E-mail: dd82109@163.com.

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Methods: Thirty-seven ESRD patients (aged 51.68±15.98 years; 43% male) on HD and 34 healthy individuals (aged 42.03±11.50 years; 38% male) were enrolled in the study. All participants underwent conventional echocardiographic examinations and 4D-LAQ. The measurements of LA dimension, volume, emptying fraction, and longitudinal/circumferential strain parameters during triphasic were obtained from the LV long axis and apical 4-chamber views, which were taken offline using software (GE EchoPac 203).

Results: In patients with ESRD, LA dimension and volume were higher than the healthy group, while the LASr (22.54±6.14 vs 33.74±5.07; p<0.05), LAScd

(-12.54±5.83 vs -20.03±5.21;p<0.05), LASct (-10.00±4.93 vs -13.56±5.17;p<0.05), LASr-c (28.00±6.61 vs 35.29±7.24;p<0.05), and LAScd-c (-13.27±5.58 vs

-18.47±8.65; p<0.05) were significantly lower. Furthermore, a good positive correlation was observed between the LAEF, LASr, and LAScd-c values and LV filling pressure, which reflect diastolic dysfunction.

Conclusion: We demonstrated that the LA strain in dialysis patients was impaired before the occurrence of LA dilation. LA strain is more sensitive than traditional echocardiographic parameters, and LASr and LAScd-c may be useful to detect early myocardial involvement.

Keywords: left atrial function; strain; end-stage renal disease; hemodialysis

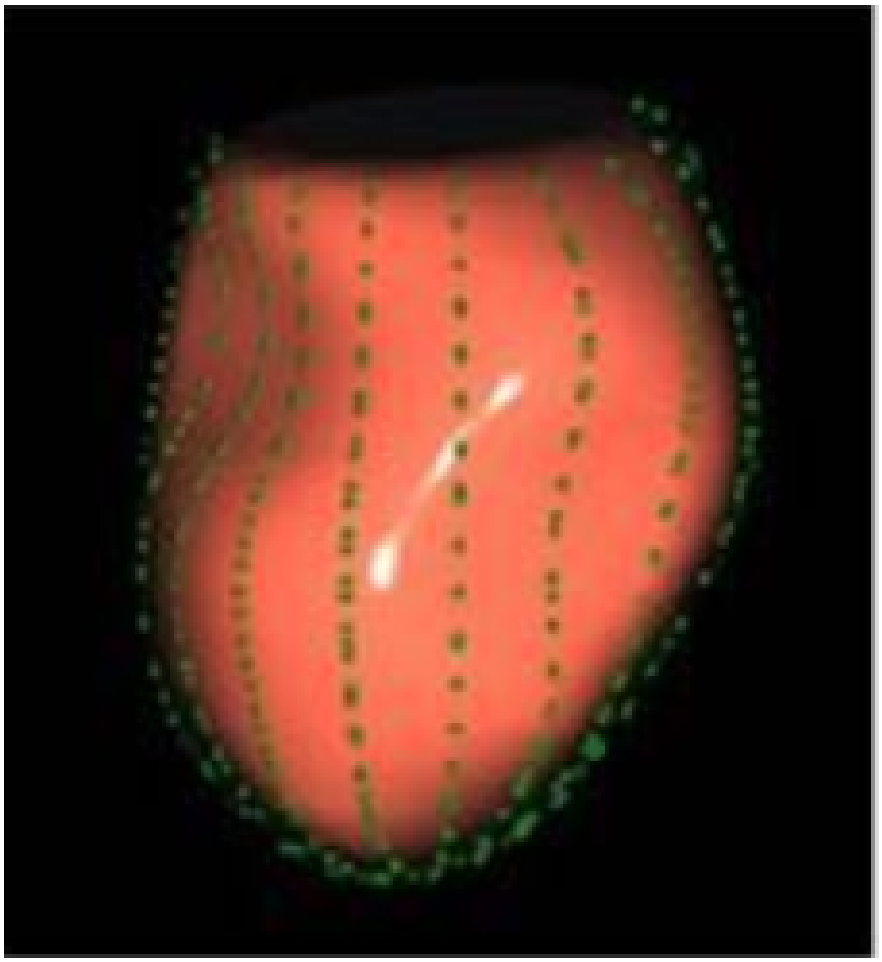
Introduction

The occurrence and development of end-stage renal disease (ESRD) is complex, which causes different degrees of damage in cardiac structure and function. Cardiovascular complication is by far the most important reason for death in patients with ESRD on hemodialysis (HD) therapy [1]. In the past, the focus of clinical research has been on the left ventricular morphology and function, but the change of left atrial (LA) function was often overlooked. Previous studies have shown that LA dilatation is closely related to the sustained volume and pressure overload, which can predict left ventricular hypertrophy, high filling pressure, and even mortality. [2] Thus, LA parameters have important clinical value in assessing the risk and prognosis of cardiovascular complications.

In clinical application, conventional echocardiography is the most common noninvasive method of evaluating cardiac structure and function in almost all patients with ESRD. However, it may not be sufficiently sensitive to detect early and subtle changes in ESRD with preserved ejection fraction, especially before serious cardiac involvement occurs. The EACVI NORRE study recently recommended the use of LA deformation imaging based on two-dimensional speckle tracking echocardiography (2D-STE)[3]. 2D-STE has been used in previous studies on LA function of this triphasic nature to document subclinical dysfunction.

Four-Dimensional Auto Left Atrial Quantification (LAQ) is a new method using three-dimensional(3D) data, which has a simple workflow and offers a new diagnosis method, evaluating the value of LA volume and emptying fraction aside from strain parameters analysis in the ESRD. LAQ can directly show LA endocardial contraction and provide sensitive and reproducible indices of myocardial dysfunction; thus, myocardial deformation was assessed directly and angle-independently [4].

The LA cavity volume is measured from a semi-automated segmentation algorithm during the cardiac cycle. The method calculates the deformation of the 3D model by solving a state estimation problem, which was constructed from an extended Kalman filter combined with LA geometry, a motion model, and edge detection algorithms. The strain is calculated based on the length change of different lines in each anatomical direction. The longitudinal strain is calculated by eight longitudinal lines from an automatically constructed triangular grid, which is connected to 2 opposite LA basal points (Figure 1). To calculate circumferential strain, 7 circumferential lines are equidistantly distributed between the LA base and apex (Figure 2).Then, strain is calculated for each frame time according to the following formula: s(t)=(L(t)-L(tref))/L(tref) X 100%, where L(t) is the line length at time t, and tref is set as the end diastolic time point of left ventricular. Global strain in each direction is obtained by calculating the average strain of the respective directional lines.



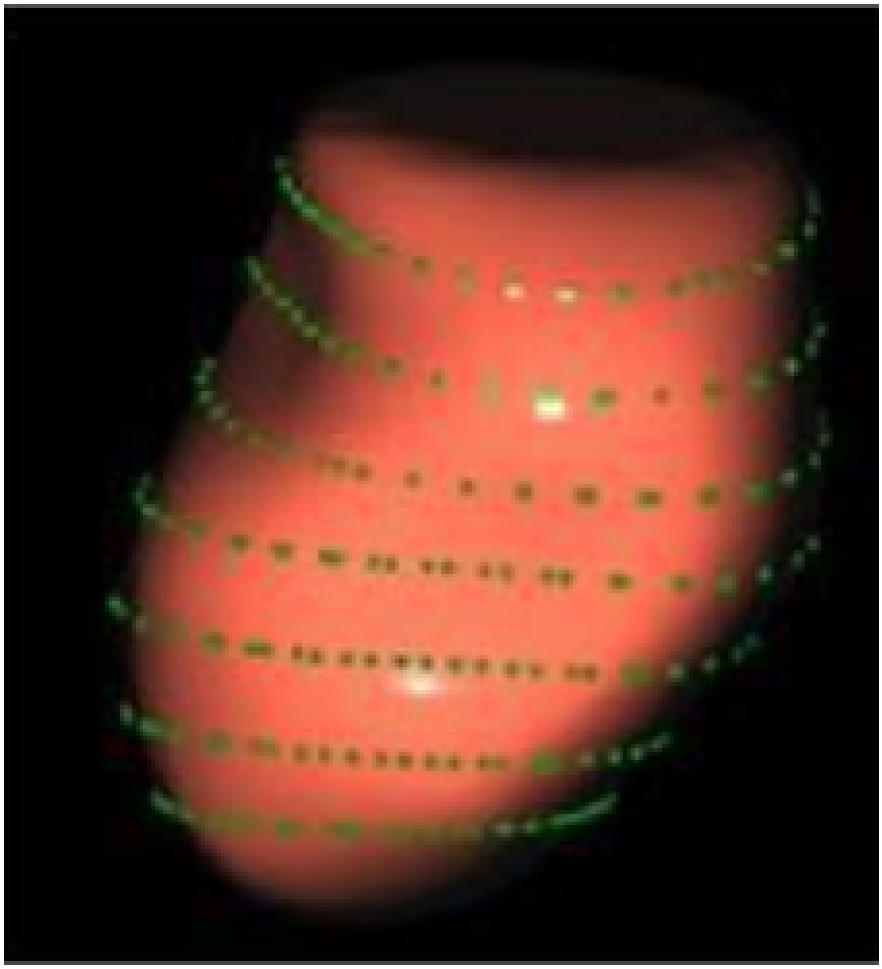


Figure 1: Points used to determine longitudinal lines.**Figure 2:** Points used to determine circumferential lines. Images were provided by GE Healthcare vendor.

2.Materials and Methods

2.1 Study Population

Every individual signed the informed consent forms approved by the Ethics Committee of our hospital. Between August 2019 and April 2020, 37 patients with ESRD on regular HD aged 51.68±15.98 years participated in this study and compared with 34 healthy control subjects, matched for sex and body surface area (BSA).

Inclusion Criteria : We used the modified National Kidney Foundation Classification of Chronic Kidney Disease, with ESRD defined as estimated glomerular filtration rate(eGFR)<15mL/min/1.73m^2, and eGFR was calculated by the MDRD formula. Adults[?]18 years old and LVEF[?]50%.**Exclusion Criteria:** Acute renal insufficiency, significant valvular heart disease, arrhythmia, severe systemic diseases, low ejection fraction (LVEF<50%) and poor echocardiographic image.

2.2 Conventional Echocardiography

Blood pressure, heart rate, and BSA measurements of all the individuals were recorded before the examination. Echocardiography was performed by an experienced cardiologist during the recovery period post-HD.

Subjects were in the left lateral decubitus position, aspirated calmly, and connected with synchronous electrocardiogram. The measurements were carried out using the echocardiography machine (Vivid E95; GE Healthcare, Horten, Norway) and a 5S (3.5-5Mhz) probe.

Images included 2D, M-mode, pulsed-, and continuous-wave Doppler in addition to Tissue Doppler Imaging (TDI) were obtained from the standard parasternal and apical positions according to the guidelines of the American Society of Echocardiography (ASE). Zoomed LA were obtained in 4-and 2-chamber views at high frame rates (60-80 frames/sec), and three consecutive cardiac cycles were stored. LAV (maximum[max], maximum[min]), 2D LAEF were measured by biplane Simpson's method. LA diameter, including antero-posterior diameter (LAD1), medial-later diameter (LAD2), and superior-inferior diameter (LAD3) were measured from left ventricular long axis and apical 4 chamber. Left ventricle end diastolic dimensions (LVEDd), interventricular septum diastolic thickness (IVST), posterior wall diastolic thickness (PWT) and LVEF were measured by M-mode method.

Left ventricle diastolic function was assessed: Peak E and A velocity were measured by pulsed-wave doppler at the mitral leaflet tips in the apical 4-chamber view, and the E/A ratio was calculated. TDI velocities early diastole (e') were recorded with the sample volume placed on the septal and lateral mitral annulus, and E/e' was calculated. Pulmonary capillary wedge pressure (ePCWP) was calculated according to the following formula: ePCWP = 1.25(E/E') + 1.9[5]. Pulmonary artery systolic pressure(PASP) was estimated with the Bernoulli equation formula: 4xTRv2 + RAP, where v is the peak tricuspid regurgitation velocity, measured by continuous-wave Doppler, added to the estimated right atrium pressure, which was calculated based on inferior vena cava (IVC) diameter and the extent of its collapse during inspiration. [6]

2.3 Four-Dimensional(4D) Auto Left Atrial Quantify

4D full volume data were acquired with a transthoracic 4D probe, and 4 consecutive cardiac cycle images from the apical 4ch view were stored in digital format, and the measurements were analyzed offline using the commercially available EchoPAC version 203 software (GE Healthcare). During the acquisition process, it is necessary to ensure that the complete LA is included, and the frame rate exceeds 12 volumes/second to obtain adequate temporal assessment and volume/EF/strain calculation.

Open 4D LA image, select Measure/volume/4D Auto LAQ in turn. First, adjust the frame control until the mitral valve closes at the Set Landmark stage. Adjust the position and angle of image according to 4 pictograms in the upper right corner of each quadrant, so that the vertical line intersects the MV center and the apex of the LA. Second, at the Review stage, the system will segment the whole volume data set to locate the endocardial borders for the LA. At the same time, the editing function includes undo/redo to locate the time frame of mitral valve opening (ES), end-diastole (ED) and preA accurately, which can be adjusted manually when the automatic tracking is not accurate. In our study, we exclude the pulmonary veins and the LA appendage. Finally, the Results stage in the worksheet and volume provides various parameters that have been calculated:

Volume and LAEF: LAVmin, LAVmax, left atrial volume at onset of contraction (LA VpreA), and LAVImax was calculated by dividing the LAVmax by BSA. Left atrial emptying volume (LAEV) was calculated by LAVmax minus LAVmin. Left atrial emptying fraction (LAEF) was calculated by dividing LA EV by LAVmax. The following left atrial strain parameters are derived:

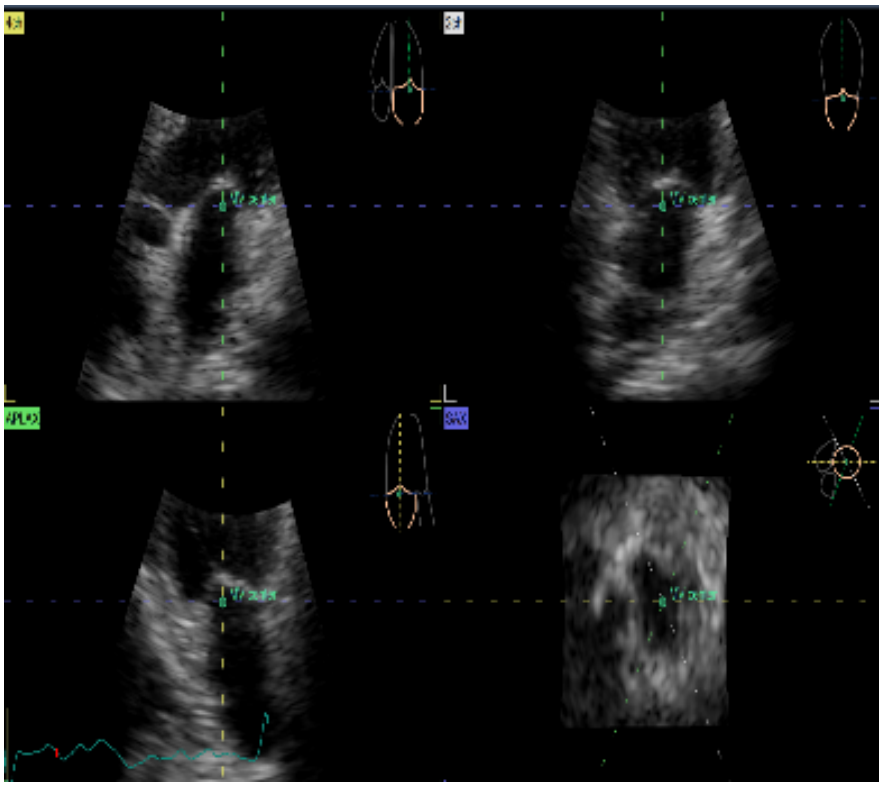
1.Reservoir phase: LA receive pulmonary veins during LV contraction, and account for approximately 40% of the atrium devoted to stroke volume. Longitudinal strain (LASr) and circumferential strain (LASr-c) are calculated by the difference of the strain value at ES minus ventricular ED. The reservoir phase encompasses the time of left ventricular isovolumic contraction, ejection and isovolumic relaxation.

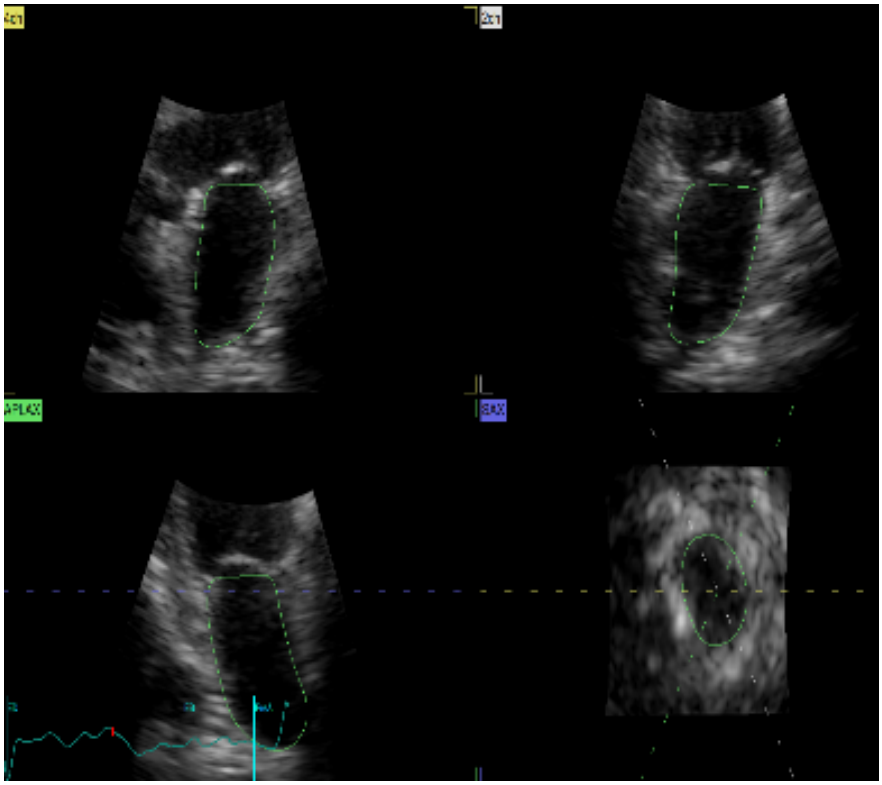
2.Conduit phase: In normal subjects, LA passively transferring blood to the LV during early diastole accounts for approximately 35% of the atrium contribution to stroke volume. Longitudinal strain (LAScd) and circumferential strain (LAScd-c) are measured as the difference of the strain value LA PreA minus ES.

3.Contraction phase: In normal subjects, LA passively transferring blood to the LV in late diastole,

account for approximately 25% of the atrium contribution to stroke volume. longitudinal strain (LASct) and circumferential strain (LASct-c) are measured as the difference of the strain value at ventricular ED minus LA-PreA only in patients in sinus rhythm.

In addition, radial strain is not involved in our study, which is related to vendor-independent software, although radial strain may account for a small proportion of LA function. We also used the global strain rather than the segmental strain because of the thin wall, which makes it difficult to obtain accurate results.





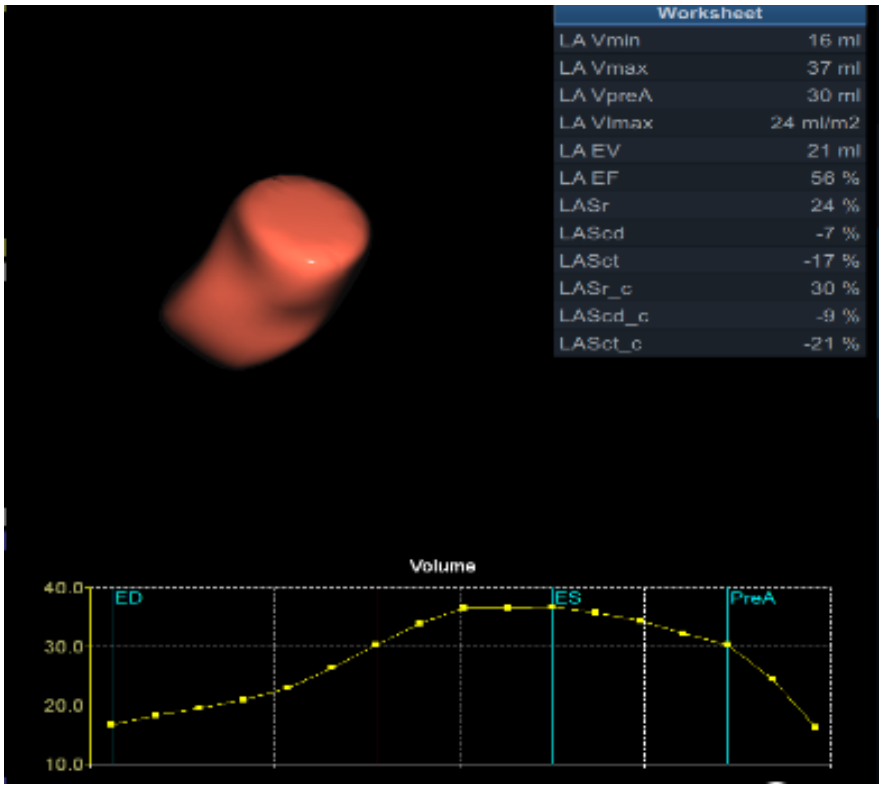


Figure 3: Set landmark on the basis of the mitral valve

Figure 4: Edit left atrial endocardial border by review stage

Figure 5: The results are displayed in worksheet and volume

2.4 Statistical Methods

The SPSS 22.0 statistical package (IBM, Armonk, NY, USA) was performed for data analyses. Continuous variables were expressed in our study as mean ± standard deviation or median (interquartile range) values. Normal distribution of the groups was tested using the Kolmogorov–Smirnov test. Continuous variables were compared using an independent-samples t-test between the 2 groups or adjusted t-test. The Pearson correlation coefficient was used to identify the correlation between the groups. Multiple linear regression analyses were performed to examine the independent correlates between 3D left atrial function and 2D conventional echocardiographic parameters in ESRD. Two-tailed P-values <.05 were considered statistically significant.

3.Results

3.1 Demographic characteristics of the study population

A total of 71 patients were enrolled in the study, of whom 37 were ESRD patients on regular HD and 34 were healthy controls. The systolic (119.94±10.32 vs 150.76±19.67; p < 0.001) and diastolic (76.68±7.03 vs 90.81±12.14; p <0.001) blood pressures were found to be higher in the ESRD group. The mean age of the ESRD group was found to be higher than the heathy group (42.03±11.50 vs 51.68±15.98, p=0.005), while no difference was observed between the groups in terms of BSA, gender, and heart rate. Laboratory tests showed an increase in serum urea (5.00±0.84 vs 17.27±5.89; p<0.001) and creatinine (63.41±12.29 vs 606.81±138.09;p<0.001) and a significant decrease in eGFR(102.40±5.36 vs 7.87±1.93;p<0.001) in the ESRD group. Among the ESRD patients, 30 had hypertension, 8 had diabetes mellitus, and 5 had hyperlipidemia (Table1).

Table 1 Baseline characteristics of the study population	**Table 1 Baseline characteristics of the study popu**
	Control Group (n=34)
Clinical Variable	
Age (years)	42.03±11.50
Gender, male	13
BSA (m2)	1.62±0.13
Systolic BP (mmHg)	119.94±10.32
Diastolic BP (mmHg)	76.68±7.03
Heart rate (bpm)	71.03±9.41
Hypertension	0
Diabetes mellitus	0
Hyperlipidemia	0
Laboratory tests	
Urea (mmol/l)	5.00±0.84
Creatinine (lmol/l)	63.41±12.29
e GFR	102.40±5.36

3.2 Traditional Echocardiographic Parameters

Of the ESRD patients on HD, 8 had mild to moderate mitral regurgitation, 12 had small pericardial effusion. Echocardiography revealed no abnormality of congenital cardiac structure. LVEDd and LV wall thickness were observed to be higher in the ESRD group while LAEF (63.41±4.97 vs 67.47±3.96; p<0.001) was lower than the heathy control, but still within in the normal range. There was a relationship between conventional

echocardiography and LV diastolic filling pressure. On the one hand, mitral late diastolic flow velocity (A), E/e' ratio, ePCWP, and PASP values were found to be higher in the ESRD group. On the other hand, the E/A ratio, mitral annulus early diastolic velocities were found to be lower in the ESRD group. In addition, no difference was observed in terms of peak E and IVC values between the groups. The results of the conventional echocardiographic parameters in both groups are presented in Table 2.

Table 2 Conventional Echocardiography Variables of Healthy Individuals and Dialysis Patients	**Table 2 Co**
Echocardiography Parameters	control grou
M-Mode and 2D	**M-Mode a**
LVEDd, mm	44.09±2.71
LV EF, %	67.47±3.96
IVST, mm	9.09±0.83
LVPWT, mm	9.24±0.61
Mitral inflow velocities	**Mitral infl**
E, cm/s	0.87±0.16
A, cm/s	0.69±0.19
E/A ratio	1.37±0.49
IVS e', m/s	0.10±0.02
LVLW e', m/s	0.13±0.03
LV diastolic filling pressure	**LV diastoli**
E/e' ratio	7.85±1.55
ePCWP, mmHg	11.72±1.93
PASP, mmHg	27.62±2.52
Inferior vena cava diameter, mm	14.18±1.03

3.3 LA structure and function parameters

The diameter and volumes of the LA, including LAVImax, LA VpreA, and LA EV by 2D- and 3D echocardiographic data were found to be higher in the ESRD group($p<0.001$). In addition, LAEF of ESRD patients was within in the normal range, but still lower than the heathy controls. Left atrial strain parameters, including longitudinal and circumferential strain values through the 4D-LAQ were observed to be lower in the ESRD group. Compared to the control group, the decrease of longitudinal strain values occurred in triphasic functions of the LA, whereas the decrease of the circumferential strain occurred in the reservoir and conduit phase. (Table 3)

Table 3 Left Atrium Functional and Structural Parameters	**Table 3 Left Atrium Functional and Structura**
	Control Group (n = 34)
2D	**2D**
LAD1, cm	29.91±1.76
LAD2, cm	37.65±4.53
LAD3, cm	45.38±5.20
LAVmax, ml	46.85±10.38
LAVmin, ml	19.18±6.01
LAEF, %	59.47±4.51
3D Left Atrial volume	**3D** Left Atrial volume
LA Vmin,ml	14.74±3.58
LA Vmax,ml	37.65±6.46
LA VpreA,ml	24.21±6.93
LAVImax,ml/m2	23.12±4.03
LA EV,ml	22.79±3.97

Table 3 Left Atrium Functional and Structural Parameters	Table 3 Left Atrium Functional and Structural
LA EF,%	61.09±5.11
3D Left Atrial strain	**3D** Left Atrial strain
LASr,%	33.74±5.07
LAScd,%	-20.03±5.21
LASct,%	-13.56±5.17
LASr-c,%	35.29±7.24
LAScd-c,%	-18.47±8.65
LASct-c,%	-16.94±7.62

3.4 Multivariate analysis for left atrial functions

We also performed multivariate analysis to determine 3D-LA volume and strain in ESRD. The relationship between PASP,

Table 4 Multivariate analysis for 3D left atrial function and 2D conventional echocardiographic variables in

3D variables
LAVmin

LAVmax

LAVpreA
LAVImax

LAEV
LAEF

SE, standard error

Discussion

HD, as a common alternative treatment for ESRD patients, can prolong the survival time of patients. Nevertheless, the high incidence of cardiovascular disease, such as heart failure and coronary heart disease, is the main cause of death. [7] Studies have shown the relationship between increased LA size, volume, and major cardiovascular events in ESRD [8]. There are many data available indicating that the diastolic function of ESRD is damaged earlier than the change of LV systolic function, and the change of LA function can more sensitively reflect the change of diastolic function. [9] The LA function can directly reflect the changes of atrioventricular pressure difference, which is the direct embodiment of left atrial preload and afterload. Thus, early detection of left atrial structural and functional impairment is helpful for the selection

of clinical treatment options in the ESRD with preserved ejection fraction on HD. In the present study, we demonstrated that LA dimension and volume increased in ESRD compared to normal healthy groups, but the strain is lower. Additionally, the strain parameters showed a better correlation with LV diastolic filling pressure than conventional parameters.

LA deformation in ESRD

In accordance with previous studies, we found that LV dimension and wall thickness increased in ESRD compared to normal healthy groups, and hypertension was found in 81% of HD group. LV hypertrophy, diastolic dysfunction, and volume overload may lead to elevated LV filling pressure and LA afterload in patients with ESRD [10] Therefore, these alterations trigger a compensatory mechanism, which is characterized by dilating and the stretching of the atrial myocardium. This contributes to an enhanced LA emptying volume activation of the Frank-Starling mechanism, which is partially responsible for the maintenance of the stroke volume in ESRD patients. [4]

The dimension and volume of LA by 2D/3D echocardiography is significantly increased, while LAEF is decreased but in the normal range. The changes in the LA functional properties were accompanied by an increase in E/e', ePCWP, PASP, and an decrease in E/A, velocities of the septal and lateral mitral annulus, peak A, which is an echocardiographic marker of LV dysfunction.

However, in the late stage of chronic renal diseases increases in the LA afterload results in LA remodeling, which is featured by increases in the LA wall thickness and focal collagen, as well as atrial myocardium fibrosis. LA remodeling is also associated with atrial interstitial fibrosis and cell hypertrophy, as well as impaired calcium uptake in the cardiomyocytes, which may contribute to the LA systolic and diastolic dysfunction [11][12][4] .With the deterioration of LA deformation, lung vessel compliance is reduced and vascular remodeling that can lead to right ventricular overload and dysfunction. [13]

LA strain in ESRD

LV diastolic dysfunction generated volume and pressure overload, which can result in LA dilation and increased pressure in ESRD patients on regular HD, may lead to a sustained elevation in LV filling pressure. Mitral E/A and E/e' ratio used to evaluate LV diastolic dysfunction by classical echocardiographers. However, they appeared late and showed variations, depending on loading situations and other conditions, such as heart rate, mitral regurgitation and so on. In addition, E/e' may be elevated in ESRD due to extracellular volume expansion.[2]

Similar to LV function, LA strain can evaluate early subclinical functional changes in ESRD. LA volume and pressure overload lead to myocardial fibrosis and compliance reduction, and then lead to left atrial remodeling and left atrial systolic function reduction, affecting the reduction of myocardial strain. Our research was concordant with other studies. The difference is the method of calculating strain. Previous studies have reported that LA strain analysis using speckle tracking echocardiography is useful for assessing LA function [14]. 3D-STI technology can track the motion track of myocardial "spot" in 3D space and construct 3D images of myocardial motion, including longitudinal strain, circumferential strain and radial strain, but the analysis of different phases is insufficient. At present, LA strain calculation is based upon the length of different lines in each anatomical direction during the three phases by 4D-LAQ.In addition, 4D LAQ have brought new insights into particular situations, which displayed LA myocardial volume and strain with high sensitivity and repeatability.

The muscle fibers of LA are predominantly arranged in 2 layers: the deep layer and the shallow layer. The shallow layer runs along the transverse diameter. The deep layer contains two kinds of myocardium, longitudinal and circular, which constitute the 3D spatial structure and complex motion of the atrium. The LA strain parameters in this study are longitudinal and circumferential strain with deep myocardial involvement only, which undertakes the most of work and is related to the vendor.

During the cardiac cycle in normal subjects, the volume contribution of ventricular filling (75-80%) mainly comes from the reservoir and conduit phase, while 20-25% comes from atrial contraction. However, the

composition of these three phases has also been redistributed when myocardial damage in ESRD. Reservoir function: In ESRD, the reduction of LV relaxation and untwisting/reverse rotation possibly leads to elevated LV filling pressure and LA pressure [15], resulting in impairment of LA compliance and relaxation. In our study, the LA longitudinal and circumferential strain during reservoir phase significantly decreased in ESRD. Moreover, the longitudinal strain revealed a strong connection with LV filling by multivariate analysis. Conduit function: The progressive worsening of LV diastolic delay and compliance reduction, LA remodeling, and diastolic function worsening leads to the reduction in the conduit phase. In our study, the LA longitudinal and circumferential strain during conduit phase showed decrease significantly in ESRD. Moreover, the circumferential strain reveals a strong connection with LV filling by multivariate analysis. Contraction function: The volume contribution of LA contraction at first compensates for the decrease in the early diastolic and diastasis phase. Lon-term exposure to accelerated volume and pressure will eventually affect the function of LA pump. Compared with the control group, our findings show that LA longitudinal strain during the contraction phase in ESRD was reduced while circumferential strain showed no significant change.

When LV diastolic function is impaired early/mild, the conduit flow is reduced while flow increases during the reservoir and pump phase [16]. With progressive worsening of diastolic function, three phases volume increases. The reason may be that RAAS system is activated to increase myocardial contractility, which is responsible for the compensation and maintenance of adequate ventricular filling through Frank-Starling mechanism. With the worsening of LA enlargement and LV diastolic dysfunction, LA strain during the three phases decreased due to the LA and LV now acting as one chamber [15]. In our study, the early damage of LA strain occurred during the reservoir and conduit phase, and contraction damage may be associated with abnormal systolic function. In conclusion, the change of LA strain is earlier than LA dimension and volume; that is, the change of function is earlier than the structuration. Moreover, LASr and LAScd-c may be associated with LV diastolic filling pressure, which is an echocardiographic marker of LV dysfunction.

Limitations

Our study has some limitations. The small size of the patient population is the main limitation. Patients were not grouped by the duration of dialysis time. This study is a single-center, small sample study; thus the promotion of the conclusion needs further multicenter large sample and long-term follow-up observation.

Conclusion

LA strain analysis may be more sensitive than conventional parameters to detect early impairment of left atrial structure and function in ESRD undergoing HD. 4D-LAQ provided a new and advanced method, we can further demonstrate and quantify these changes, even in the early stage of the disease process.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure 1. Points used to determine longitudinal lines.

Figure 2. Points used to determine circumferential lines.

Figure 3. Set landmark on the basis of the mitral valve

Figure 4. Edit left atrial endocardial border by review stage

Figure 5. The results are displayed in worksheet and volume

Table 1. Baseline characteristics of the study population

Table 2. Conventional Echocardiography Variables of Healthy Individuals and Dialysis Patients

Table 3. Left Atrium Functional and Structural Parameters

Table 4. Multivariate analysis for 3D left atrial function and 2D conventional echocardiographic variables in ESRD