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Comparison of left atrial deformation parameters between renal transplant and hemodialysis patients

Ufuk Yildirim^{1*}, Murat Akcay¹, Metin Coksevim¹, Ercan Turkmen² and Okan Gulel¹

Abstract

Background: Renal transplantation (RT) has been demonstrated to improve left ventricular systolic function. However, only few studies have attempted to reveal the effects of transplantation on left atrial (LA) function. In our study, we aimed to compare LA function between RT and hemodialysis patients.

Methods: This cross-sectional study included 75 consecutive patients with RT, and 75 age- and gender-matched patients on maintenance hemodialysis. LA strain and strain rate (SR) analyzed by two-dimensional (2D) speckle tracking echocardiography (STE) were compared between the groups in addition to standard echocardiographic parameters.

Results: LA strain during reservoir phase (29.88 \pm 5.76% vs 26.11 \pm 5.74%, P < .001), LA strain during conduit phase (- 15.28 \pm 5.00% vs - 12.92 \pm 4.38%, P = .003), and LA strain during contraction phase (- 14.60 \pm 3.32% vs - 13.19 \pm 3.95%, P = .020) were higher in the transplantation group. Similarly, LA peak SR during reservoir phase (1.54 \pm 0.33 s⁻¹ vs 1.32 \pm 0.33 s⁻¹, P < .001), LA peak SR during conduit phase (- 1.47 \pm 0.49 s⁻¹ vs - 1.12 \pm 0.42 s⁻¹, P < .001), and LA peak SR during contraction phase (- 2.13 \pm 0.46 s⁻¹ vs - 1.83 \pm 0.58 s⁻¹, P = .001) were higher in the transplantation group as well.

Conclusions: LA function assessed by 2D STE was better in RT patients than hemodialysis patients. This may suggest favorable effects of RT on LA function.

Keywords: Renal transplantation, Hemodialysis, Speckle tracking echocardiography, Left atrial function, Strain, Strain rate

Introduction

It is well established that chronic kidney disease (CKD) is associated with important cardiac alterations such as left ventricular (LV) hypertrophy, LV systolic and diastolic dysfunction, LV and left atrial (LA) dilatation [1, 2]. Even though structural cardiac alterations are initially adaptive, they may progress over time and lead to cardiac dysfunction [1]. Renal transplantation (RT) has reduced the

risk of CV death compared with long-term dialysis [3]. In addition, LV systolic function tends to improve after RT in patients with end-stage renal disease (ESRD) [1, 4, 5]. However, only few studies have attempted to reveal the effects of RT on LA function.

Two-dimensional (2D) speckle tracking echocardiography (STE) has been well validated as a quantitative tool to evaluate LV function [6]. This modality has also been applied to assess LA function. During the cardiac cycle, LA has three main functions: reservoir function in systole when blood fills LA, conduit function in early diastole corresponding to passive LV filling, and active contractile function in late diastole [7]. LA deformation

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parameters analyzed by STE provide a window on all phases of LA function [8]. CKD is an independent factor affecting LA function [9]. In our study, we aimed to compare LA deformation parameters between RT and hemodialysis patients.

Methods

Study population

A total of 150 patients with CKD followed up at the Nephrology Outpatient Clinic were included into this cross-sectional study, and two groups were formed. Seventy-five consecutive patients with RT having a functional graft >1 year and estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m² were compared with 75 age- and gender-matched patients receiving hemodialysis three times per week. Modification of Diet in Renal Disease formula was used to calculate eGFR.

Exclusion criteria were as follows: age < 18 years or > 65 years, body mass index \geq 40 kg/m², clinical symptoms and signs of hypervolemia, LV ejection fraction (LVEF) < 45%, documented ischemic heart disease, moderate to severe heart valve disease or history of heart valve surgery, hypertrophic or restrictive cardiomyopathy, constrictive pericarditis, atrial fibrillation, QRS duration \geq 120 ms, history of RT rejection, and poor echocardiographic image quality.

The study was approved by the institutional ethics committee. Informed consent was obtained from all participants included in the study.

Echocardiography

Echocardiography was performed using a Vivid E9 echocardiography machine (GE Vingmed Ultrasound, Horten, Norway) and M5S ultrasound probe (1.5–4.5 MHz). All echocardiograhic examinations were made by the same physician at midday to avoid circadian changes. For the patients on maintenance hemodialysis, echocardiographic measurements were performed on the next day after dialysis treatment [10].

Cardiac chamber dimensions were measured in accordance with the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [11]. Linear internal dimensions of LV and its walls were acquired in the parasternal long-axis view and measured at the level of the mitral valve leaflet tips directly from 2D echocardiographic images. LV mass was calculated using the Devereux's formula and indexed to body surface area (BSA). LVEF was estimated using modified Simpson method. LA anteroposterior diameter (LAAPD) was obtained in the parasternal long-axis view and measured at the level of the aortic sinuses from 2D echocardiographic images. LA volume was calculated using biplane area-length method and indexed

to BSA. Pulmonary artery systolic pressure (PASP) was estimated by using the formula based on tricuspid regurgitant jet velocity, inferior vena cava diameter and collapsibility. Pulsed-wave (PW) Doppler was performed between mitral leaflet tips in the apical 4-chamber view to acquire mitral inflow velocities and PW tissue Doppler imaging was performed at the septal and lateral border of mitral annulus in the apical 4-chamber view to acquire average mitral annular velocities. Peak velocity of early mitral inflow (mitral E), peak velocity of late mitral inflow (mitral A), ratio of mitral E to mitral A (mitral E/A), peak systolic velocity of mitral annulus (mitral s'), peak early diastolic velocity of mitral annulus (mitral e'), peak late diastolic velocity of mitral annulus (mitral a'), and ratio of mitral E to mitral e' (mitral E/e') were obtained.

Two-dimensional speckle tracking analysis of left atrium

For 2D speckle tracking analysis of LA, apical 4-chamber and 2-chamber view images were acquired at a frame rate of 60-80 frames/s. Three consecutive cardiac cycles were recorded in each view for offline analysis using the software (EchoPac PC, version 110.1.2, GE Vingmed Ultrasound, Horten, Norway). LA deformation parameters were analyzed by another physician blinded to the patient's clinical status. We used P wave onset of the electrocardiogram as the reference point to calculate LA strain and strain rate (SR), as previously recommended in sinus rhythm [12]. Using P wave as the reference point enabled to identify LA strain during contraction phase (LASct), LA strain during conduit phase (LAScd), and LA strain during reservoir phase (LASr) (Fig. 1). Similarly, we specified LA peak SR during contraction phase (pLASRct), LA peak SR during reservoir phase (pLASRr), and LA peak SR during conduit phase (pLASRcd) (Fig. 2).

A spesific cardiac cycle was selected for each view, and LA endocardial surface was manually traced in both apical 4-chamber and 2-chamber view images by a point-and-click approach. Epicardial surface tracing was automatically created by the system, forming a region of interest (ROI), which could be manually adjusted in width and shape. ROI was divided into 6 segments by the software in each view. Segments without adequate image quality for speckle tracking analysis were excluded from the evaluation by the system. The average values of LA deformation parameters for each apical view were calculated, and the final values were the averages of the ones calculated for each apical view.

Intraobserver and interobserver variability

Intraobserver and interobserver variability for LA deformation parameters were evaluated by re-analyzing the recorded images of 12 randomly selected patients with 6 subjects from each group. Speckle tracking

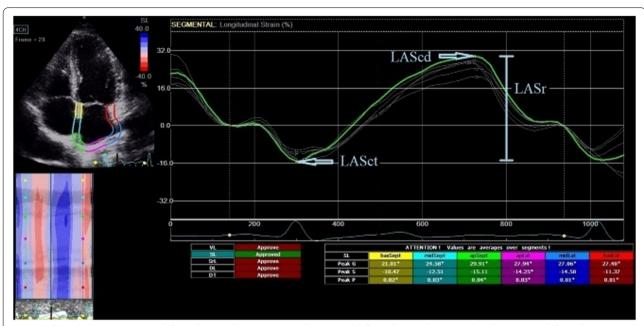


Fig. 1 Left atrial strain curves. LASr, left atrial strain during reservoir phase; LAScd, left atrial strain during conduit phase; LASct, left atrial strain during contraction phase

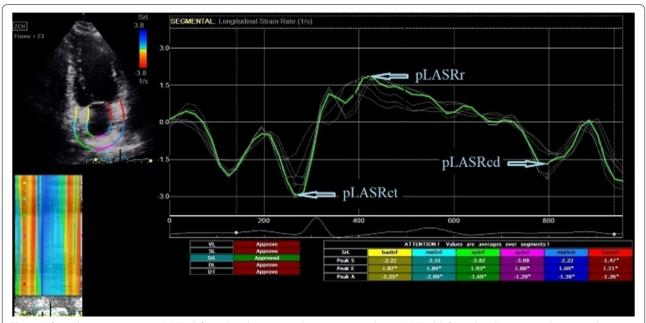


Fig. 2 Left atrial strain rate curves. pLASRr, left atrial peak strain rate during reservoir phase; pLASRcd, left atrial peak strain rate during conduit phase; pLASRct, left atrial peak strain rate during contraction phase

analyzes were repeated by the same individual after at least 1 week for intraobserver variability and by another physician for interobserver variability.

Statistical analysis

The research data were uploaded and evaluated by using IBM Statistical Package for Social Sciences version 25. Descriptive statistics for categorical variables were

reported as frequencies and percentages. Pearson Chi Square was used to compare categorical variables in addition to descriptive statistics. The suitability of numerical variables with normal distribution was determined by visual (histograms and probability plots) and analytical (Kolmogorov-Smirnov and Shapiro-Wilk tests) methods. Descriptive statistics for numerical variables with normal distribution were reported as mean \pm standard deviation. Independent Samples t test was used for the variables with normal distribution to identify significant differences between the groups and Levene's test was applied to determine homogeneity of variances. Descriptive statistics for numerical variables without normal distribution were reported as median (minimum-maximum). Mann-Whitney U test was used for comparisons of variables without normal distribution. When comparing LA deformation parameters between RT and hemodialysis patients in Table 3, analysis of covariance (ANCOVA) was also performed to control the effects of systolic blood pressure (SBP), serum hemoglobin level, and LVEF on the outcomes. Pearson correlation coefficient was used to measure the magnitude and direction of the relationships between numerical variables with normal distribution, and Spearman correlation coefficient was used for numerical variables without normal distribution. $R \ge 0.7$ was defined as strong relationship, $0.5 \le R < 0.7$ was defined as moderate relationship, and $0.3 \le R < 0.5$ was defined as weak relationship. Intraobserver and interobserver variability were assessed using intraclass correlation coefficient (ICC) by Cronbach. Statistical significance level was accepted as P < 0.05.

Results

Baseline characteristics of the study population

Baseline characteristics of the study population are presented in Table 1. There was no significant difference

between the groups in terms of age, gender, diastolic blood pressure (DBP), heart rate, history of hypertension, duration of hypertension, history of diabetes mellitus, and duration of diabetes mellitus. SBP was significantly higher in the hemodialysis group (P < .001). Median time of CKD duration was longer in the transplantation group (P = .015). Median time of CKD duration before RT was 5 (1–19) years, median time of dialysis treatment before RT was 3 (1–15) years, and median time after RT was 3 (1–12) years in the transplantation group. Median time after the initation of dialysis treatment was 3 (1–20) years in the hemodialysis group. Serum hemoglobin level was significantly higher in the transplantation group (P < .001).

Standard echocardiographic parameters

LV diastolic diameter (LVDD), LV systolic diameter (LVSD), septal wall thickness (SWT), posterior wall thickness (PWT), and LV mass index (LVMi) were significantly lower in the transplantation group compared to the hemodialysis group (P = .004, P < .001, P = .001, and P < .001, respectively). LVEF was significantly higher in the transplantation group (P < .001). LAAPD and LA volume index (LAVi) were significantly lower in the transplantation group than the hemodialysis group (P < .001 for each) (Table 2).

Mitral E, mitral E/A, and PASP did not significantly differ between the groups. Mitral A and mitral E/e' were significantly lower in the transplantation group compared to the hemodialysis group (P < .001 for each). Mitral s', mitral e', and mitral a' were significantly higher in the transplantation group (P < .001, P = .001, and P = .003, respectively) (Table 2).

Left atrial deformation parameters

LASr, LAScd, and LASct were significantly higher in the transplantation group compared to the hemodialysis

Table 1 Baseline characteristics of the study population

Variable	Transplantation group	Hemodialysis group	Р	
Age (year)	41.3 ± 10.5	43.3 ± 10.6	.257	
Male (% ^a)	39 (52.0)	37 (49.3)	.870	
SBP (mmHg)	123.5 ± 15.0	133.2 ± 17.5	<.001	
DBP (mmHg)	78.2 ± 9.2	80.4 ± 10.2	.167	
Heart rate (beats/min)	80.3 ± 11.7	79.3 ± 13.1	.637	
History of hypertension (%a)	58 (77.3)	64 (85.3)	.295	
Duration of hypertension (year)	8 (1–20)	8 (1–25)	.429	
History of diabetes mellitus (%a)	13 (17.3)	14 (18.7)	.832	
Duration of diabetes mellitus (year)	9.0 ± 5.9	12.7 ± 6.8	.142	
Duration of CKD (year)	10 (3–25)	7 (1–24)	.015	
Serum hemoglobin level (g/dL)	13.71 ± 1.84	12.02 ± 1.50	<.001	

^a Column percentage

Yildirim et al. Cardiovascular Ultrasound (2022) 20:5 Page 5 of 8

Table 2 Standard echocardiographic parameters

Variable	Transplantation group	Hemodialysis group	P	
LVDD (mm)	43 (36–58)	48 (34–58)	.004	
LVSD (mm)	26 (19–43)	32 (19–45)	<.001	
SWT (mm)	12 (7–17)	13 (7–17)	.001	
PWT (mm)	10 (7–15)	12 (7–17)	.001	
LVMi (g/m²)	96.8 ± 25.2	130.5 ± 41.2	<.001	
LVEF (%)	66.6 ± 5.7	59.8 ± 6.5	<.001	
LAAPD (mm)	33 (26–45)	37 (25–45)	<.001	
LAVi (mL/m²)	23 (13–55)	34 (13–60)	<.001	
Mitral E (cm/s)	83.7 ± 19.8	88.3 ± 25.1	.219	
Mitral A (cm/s)	79.9 ± 16.6	90.0 ± 18.0	<.001	
Mitral E/A	1.1 (0.5–1.6)	0.9 (0.5-1.6)	.070	
Mitral s' (cm/s)	9 (6–15)	7 (5–12)	<.001	
Mitral e' (cm/s)	10.1 ± 3.0	8.4 ± 2.7	.001	
Mitral a' (cm/s)	10 (7–18)	9 (5–17)	.003	
Mitral E/e'	8.1 (4.7–18.0)	10.8 (4.2–24.5)	<.001	
PASP (mmHg)	26.9 ± 6.8	28.3 ± 7.7	.229	

Table 3 Left atrial deformation parameters

Variable	Transplantation	Hemodialysis	P	P*	
	group	group			
LASr (%)	29.88 ± 5.76	26.11 ± 5.74	<.001	.014	
LAScd (%)	-15.28 ± 5.00	-12.92 ± 4.38	.003	.030	
LASct (%)	-14.60 ± 3.32	-13.19 ± 3.95	.020	.274	
$pLASRr(s^{-1})$	1.54 ± 0.33	1.32 ± 0.33	<.001	.006	
pLASRcd (s^{-1})	-1.47 ± 0.49	-1.12 ± 0.42	<.001	.001	
$pLASRct(s^{-1})$	-2.13 ± 0.46	-1.83 ± 0.58	.001	.076	

^{*} After adjustment for SBP, serum hemoglobin level, and LVEF

group (P < .001, P = .003, and P = .020, respectively). Similarly, pLASRr, pLASRcd, and pLASRct were significantly higher in the transplantation group (P < .001, P < .001, and P = .001, respectively) as well. After adjusting for SBP, serum hemoglobin level, and LVEF, statistical significance was preserved except for LASct and pLASRct (P = .274 and P = .076, respectively) (Table 3).

When considering only strong and moderate relationships; LASr had a positive moderate correlation with mitral e' (R = .608, P < .001), LAScd had a positive moderate correlation with mitral e' (R = .674, P < .001), pLASRcd had a positive strong correlation with mitral e' (R = .766, P < .001) and a negative moderate correlation with PWT (R = -.506, P < .001). Many more significant but weak relationships were also detected between LA deformation parameters and standard echocardiographic parameters (Table 4).

ICC analysis of intraobserver and interobserver variations for LA deformation parameters is presented in Table 5.

Discussion

In the present study, the comparison between RT and hemodialysis patients revealed that LASr, LAScd, and LASct were significantly higher in patients with RT than patients on maintenance hemodialysis. We also demonstrated that pLASRr, pLASRcd, and pLASRct were significantly higher in RT patients as well. LVEF and serum hemoglobin level were significantly higher, SBP was significantly lower in RT recipients in accordance with the literature [4]. Nevertheless, in order to understand whether the results are just the reflection of higher LVEF in the transplantation group and to control the possible effects of serum hemoglobin level and SBP on LA deformation parameters, adjusted P values were obtained. After adjusting for LVEF, serum hemoglobin level, and SBP, statistical significance was preserved for parameters indicating LA reservoir and conduit function, but no longer present for parameters indicating LA contractile function. In addition, we detected many significant relationships between LA deformation parameters and standard echocardiographic parameters, one of which was the strong correlation between mitral e' and pLASRcd.

LA size and function are important predictors of CV morbidity and mortality in patients with CKD [13]. During the cardiac cycle, LA has three main functions. Reservoir function corresponding to LV isovolumic contraction, ejection, and isovolumic relaxation is influenced by LV systolic function, atrial size and compliance. Conduit function corresponding to early transmitral flow is influenced by atrial compliance, LV relaxation and compliance. Lastly, contractile function corresponding to late transmitral flow is influenced by atrial contractility, atrial preload, atrial afterload, and LV systolic reserve [14]. The alterations of LA size and function in patients with CKD are multifactorial. LV hypertrophy, LV diastolic dysfunction, and volume overload may cause increased LV filling pressure and LA afterload in these patients [13]. These alterations prompt a compensatory mechanism in LA characterised by LA dilatation [15]. Late stage chronic increases in LA afterload in addition to LA remodelling may prompt the alterations in the compliance, reservoir function, and contractile function of LA [10]. LA remodelling is also associated with atrial interstitial fibrosis and cell hypertrophy, which may contribute to impaired LA function [16]. It has been demonstrated that LA deformation parameters assessed by STE provide a better diagnostic performance in indicating subclinic LA dysfunction in patients with CKD as compared to the Doppler parameters which have been shown to be very preload-dependent [17, 18]. Even though LAVi is less affected by preload [19], it cannot accurately represent LA function [20]. The abnormalities in LA deformation

Yildirim et al. Cardiovascular Ultrasound (2022) 20:5 Page 6 of 8

Table 4 Correlation analysis

Variable	LASr		LAScd		LASct		pLASRr		pLASRcd		pLASRct	
	R	P	R	P	R	Р	R	Р	R	P	R	Р
LVDD	139	.093	002	.977	269	.001	187	.023	164	.047	260	.001
LVSD	238	.004	085	.304	328	<.001	197	.016	215	.009	349	<.001
SWT	241	.003	294	<.001	.002	.984	227	.005	418	<.001	117	.158
PWT	333	<.001	345	<.001	099	.230	312	<.001	506	<.001	233	.004
LVMi	315	<.001	230	.005	214	.009	357	<.001	402	<.001	270	.001
LVEF	.262	.001	.123	.138	.309	<.001	.160	.052	.179	.029	.326	<.001
LAAPD	324	<.001	214	.009	282	.001	322	<.001	419	<.001	362	<.001
LAVi	327	<.001	212	.010	292	<.001	357	<.001	404	<.001	421	<.001
Mitral E	.154	.062	.294	<.001	213	.009	120	.146	.208	.011	204	.013
Mitral A	.009	.913	109	.187	.174	.034	.053	.525	238	.004	.056	.500
Mitral E/A	.119	.149	.355	<.001	337	<.001	158	.056	.366	<.001	237	.004
Mitral s'	.369	<.001	.371	<.001	.130	.116	.486	<.001	.464	<.001	.336	<.001
Mitral e'	.608	<.001	.674	<.001	.112	.176	.418	<.001	.766	<.001	.313	<.001
Mitral a'	.162	.049	072	.382	.413	<.001	.408	<.001	049	.554	.459	<.001
Mitral E/e'	413	<.001	390	<.001	172	.037	451	<.001	498	<.001	395	<.001
PASP	090	.276	037	.653	098	.235	253	.002	121	.144	137	.097

Table 5 Intraobserver and interobserver variability

Variable	Intraobserv	er variation		Interobserver variation				
	ICC	95% CI	P	ICC	95% CI	P		
LASr	0.987	0.955-0.996	<.001	0.985	0.947-0.996	<.001		
LAScd	0.978	0.924-0.994	<.001	0.960	0.862-0.989	<.001		
LASct	0.966	0.882-0.990	<.001	0.973	0.905-0.992	<.001		
pLASRr	0.938	0.786-0.982	<.001	0.893	0.628-0.969	<.001		
pLASRcd	0.991	0.969-0.997	<.001	0.979	0.928-0.994	<.001		
pLASRct	0.957	0.852-0.988	<.001	0.970	0.895-0.991	<.001		

CI Confidence interval

parameters are relatively independent from LA dilatation and volume overload [21], so the alterations in LA strain and SR may precede the alterations in LA volume [22]. Kadappu et al. demonstrated that LA strain was the most significant and sensitive parameter to detect myocardial involvement in patients with CKD [23].

Few studies have attempted to reveal the effects of RT and hemodialysis on LA size and function. It has been reported that there may be a reduction in LA size after RT in patients with ESRD [24, 25]. However, in the study of Hewing et al. evaluating 31 RT recipients by echocardiography before and after RT with a median follow-up of 19 months, LAVi and LA strain analyzed by STE did not change significantly after RT. [1] In our study in which median time after RT was 3 years in the transplantation group, RT recipients had better outcomes in terms of LAVi and LA deformation parameters compared

to hemodialysis patients. Successful RT in patients with uremic cardiomyopathy initiates the process of LA recovery in long-term clinical observation [26]. It is obvious that further studies are required to clarify this issue.

It has been reported that patients with ESRD have altered LA function [15, 17, 27] and LA strain values tend to decrease as systolic and diastolic LV function deteriorate [28]. ESRD is a complex metabolic disorder that can cause cardiac structural and functional changes known as uremic cardiomyopathy. Long-term exposure to uremic toxins leads to fibrosis and death of myocytes in addition to potentially negative inotropic and chronotropic effects [29]. With elimination of uremic environment after successful RT, uremia-specific CV risk factors such as inflammation, oxidative stress, endothelial dysfunction, anemia, abnormal calcium-phosphorous metabolism, and secondary hyperparathyroidism can improve

in patients with ESRD [30]. These patients may have an improvement in blood pressure, LV mass, and LV systolic function after RT. [1, 4] On the other hand, increased oxidative stress and sympathetic activation, impaired endothelial function, and volume load between hemodialysis sessions are some of the factors which increase the likelihood of CV disease in hemodialysis patients [31]. These factors may be associated with the different effects of RT and hemodialysis on LV and LA function.

In the present study, further differences in addition to LA deformation parameters were detected between the groups. SBP was lower in the transplantation group. It has been reported that patients with ESRD may experience an improvement in SBP after successful RT. [1] Consistent with the literature [4], RT recipients in our study had higher serum hemoglobin level compared to patients on maintenance hemodialysis. LVMi was also lower in patients with RT, in line with the previous studies [1, 4, 32, 33]. LV systolic function tends to improve after RT. [1, 4, 5] Despite longer CKD duration, RT recipients had higher LVEF in the present study. In a study comparing Doppler and tissue Doppler echocardiographic parameters between 30 patients with RT and 30 patients with ESRD; mitral E/A, s', e', a' tended to be higher in patients with RT, but mitral A tended to be higher in patients with ESRD [34]. Similarly, in our study comparing 75 patients with RT and 75 patients on maintenance hemodialysis; mitral s', e', a' were significantly higher in the transplantation group, mitral E/A tended to be higher in the transplantation group (P = .070), mitral A was significantly higher in the hemodialysis group, and mitral E/e' was also significantly higher in the hemodialysis group.

Our findings imply that successful RT may be associated with an improvement in LA deformation parameters which have been demonstrated to be the best predictor of CV outcomes in patients with CKD [35]. Among the standard echocardiographic parameters, mitral e's hows the best correlation with LA deformation parameters, particularly with the ones indicating LA reservoir and conduit function. In addition, RT may lead to an improvement not only in LV systolic function but also in LV diastolic function.

To the best of our knowledge, this is the first study to present data regarding LA SR values in patients undergoing RT. SR has been shown to be less affected by loading conditions compared to strain [36]. Therefore, evaluation of LA SR may provide additional information for the assessment of LA function in patients with CKD. Moreover, this study reveals the most comprehensive correlation analysis between LA deformation parameters and standard echocardiographic parameters.

The present study has also some limitations. This cross-sectional study was not a follow-up study. We did

not have echocardiographic data of the patients before the initiation of hemodialysis and RT. Even though the sample size of the study was relatively small, significant differences were observed between the groups. Patients with clinical symptoms and signs of hypervolemia were excluded, but invasive measurements were not performed for the assessment of volume status.

Conclusions

LA function assessed by 2D STE was better in patients with RT than patients on maintenance hemodialysis. This may suggest favorable effects of RT on LA function.

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Authors' contributions

All authors made substantial contributions to the study conception and design; acquisition, analysis and interpretation of the data. The draft of the manuscript was written by Ufuk Yildirim and approved by all authors.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by Ondokuz Mayis University Clinical Research Ethics Committee. Informed consent was obtained from all participants included in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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