







To cite this article: Elcioglu Cengiz B, Baydar O, Kılıc A, Yelken B, Aytekin V, Aytekin S. Evaluation of left atrial appendage functions by transthoracic echocardiography and comparison with left atrial strain values in renal transplant candidates . Turk J Clin Lab 2023; 3: 599-607

■ Research Article

Evaluation of left atrial appendage functions by transthoracic echocardiography and comparison with left atrial strain values in renal transplant candidates

Böbrek nakli adaylarında transtorasik ekokardiyografi ile sol atriyal apendiks fonksiyonlarının değerlendirilmesi ve sol atriyal strain değerleri ile karşılaştırılması

 Betül Cengiz Elcioglu*¹,  Onur Baydar¹,  Alparslan Kılıc¹,  Berna Yelken²,  Vedat Aytekin¹,
 Saide Aytekin¹

¹Koç University Hospital, Department of Cardiology, Istanbul, Turkey

²Koç University Hospital, Organ Transplant Center, Istanbul, Turkey

Abstract

Aim: The incidence of stroke in patients with chronic kidney disease (CKD) is increased independent of atrial arrhythmias. The goal of this study is to evaluate, left atrial appendage (LAA) functions by transthoracic echocardiography (TTE) and comparison with left atrial (LA) strain values in patients with in renal transplant candidates with end stage renal disease (ESRD) with sinus rhythm.

Material and Methods: Fifty two renal transplant candidates and 60 age- and sex-matched healthy participants were included in the study. LAA emptying velocity (EV) was measured with pulse wave Doppler, early diastolic (LAA Em), contraction (LAA Am) and systolic (LAA Sm) velocities were measured using tissue Doppler imaging from parasternal short axis view. Atrial peak longitudinal strain (PLS), peak contraction strain (PCS) and conduit strain (CdS) were calculated using two dimensional speckle tracking echocardiography.

Results: LAA EV, Am and Sm and LA PLS, PCS, CdS measurements were found to be significantly lower in the patient group compared to controls. LAA EV measurements showed a strong positive correlation with left atrial volume index (LAVI), LA PLS and LA PCS values, and a negative correlation with left ventricular (LV) diameters, and E/e' value. In the multivariate regression analysis LA PLS and LAVI were found to be independent factors for LAA EV.

Conclusion: Our findings suggest that the evaluation of LAA functions with TTE may help determine the increased risk of developing atrial arrhythmias and ischemic stroke in renal transplant candidates. Supporting the current findings with larger studies may change the follow-up and treatment approaches in these patients.

Keywords: Left atrial strain, left atrial appendage functions, end stage renal disease, kidney transplantation.

Corresponding Author*: Betül Cengiz Elcioglu, Koç University Hospital, Department of Cardiology, Istanbul, Turkey.

Orcid: 0000-0002-9310-3767

E-mail: betulcengiz@yahoo.com

Doi: 10.18663/tjcl.1268990

Received: 23.03.2023 accepted: 26.08.2023

Öz

Amaç: Kronik böbrek hastalığı (KBH) olan hastalarda inme insidansı,atriyal aritmilerden bağımsız olarak yüksektir. Bu çalışmanın amacı, sinüs ritmindeki son dönem böbrek hastalığı (SDBY) olan böbrek nakli adaylarında transtorasik ekokardiyografi (TTE) ile sol atriyal apendiks (SAA) fonksiyonlarını değerlendirmek ve sol atriyal (SA) strain değerleri ile karşılaştırmaktır.

Gereç ve Yöntemler: Çalışmaya 52 böbrek nakli adayı hasta ve yaş ve cinsiyet uyumlu, KBH olmayan 60 katılımcı dahil edildi. Parasternal kısa eksen pulse wave Doppler ile SAA boşalma hızı (BH), doku Doppler görüntüleme kullanılarak erken diyastolik (SAA Em), kasılma (SAA Am) ve sistolik (SAA Sm) hızları ölçüldü. Atriyal pik longitudinal strain (PLS), pik kontraksiyon strain (PKS) ve konduit strain (KdS), iki boyutlu "speckle tracking" ekokardiyografi kullanılarak hesaplandı.

Bulgular: SAA BH, Am ve Sm ve SA PLS, PKS, KdS ölçümleri hasta grubunda kontrollere göre anlamlı olarak daha düşük bulundu. SAA BH ölçümleri, sol atriyal volüm indeksi (SAVİ), SA PLS ve SA PKS değerleri ile güçlü bir pozitif korelasyon ve sol ventrikül (SV) çapları ve E/e' değeri ile de anlamlı negatif korelasyon gösterdi. Çok değişkenli regresyon analizinde SA PLS ve SAVİ'nin SAA BH için bağımsız faktörler olduğu bulundu.

Sonuçlar: Bulgularımız, TTE ile SAA fonksiyonlarının değerlendirilmesinin böbrek nakil adaylarında artmış atriyal aritmiler ve iskemik inme gelişme riskinin belirlenmesine yardımcı olabileceğini düşündürmektedir. Mevcut bulguların daha büyük çalışmalarla desteklenmesi bu hastalarda takip ve tedavi yaklaşımlarını değiştirebilir.

Anahtar kelimeler: Sol atriyal strain, sol atriyal apendiks fonksiyonu, son dönem böbrek yetersizliği, böbrek nakli.

Introduction

Cardiovascular disorders (CVD) are common in chronic kidney disease (CKD) and the major cause of morbidity and mortality in patients with end stage renal disease (ESRD) [1]. Fluid retention, hormones, cytokines and enzymes released in response to kidney failure constitute the main causes of CV pathologies in these patients along with the common risk factors [2, 3]. Arterial stiffness, myocardial fibrosis, left ventricular hypertrophy (LVH), enlargement of the heart chambers, LV diastolic and systolic dysfunction may develop over time with the contribution of all these factors [4, 5].

The incidence of stroke in CKD patients is increased compared to the general population, especially in patients on dialysis [6]. Although atrial fibrillation (AF) is one of the major causes of ischemic stroke, a significant number of patients with ischemic cerebrovascular event (CVE) are in sinus rhythm [7]. There are studies showing that left atrial (LA) size and functions are associated with the risk of ischemic stroke independent of AF rhythm [8]. Most of the thrombi that develop in the left atrium are located in the left atrial appendage (LAA) [9]. Therefore, the evaluation of LAA functions has gained importance in determining the risk of ischemic stroke.

Cardiac structural and functional changes affect LA functions in patients with CKD [10]. Apart from atherosclerotic vascular changes and AF, which are the most important causes of ischemic stroke in these patients, impaired LA and LAA functions may also increase the risk of stroke. Transesophageal echocardiography (TEE) is the most sensitive method to assess LAA functions [11]. However, recent studies have revealed that the LAA evaluation with transthoracic echocardiography (TTE), which is a more feasible method, also correlates well with the TEE measurements [12]. The aim of this study is to evaluate the functions of LA and LAA with TTE in kidney transplantation candidates.

Material and Methods

Study design and patient selection

Our study was designed prospectively, and 52 patients with ESRD and 60 healthy participants who were similar regarding age and gender were included in the study. The patient group was selected from ESRD patients who were planned for kidney transplantation and referred to the cardiology outpatient clinic for preoperative evaluation. The control group consisted of participants without heart failure and kidney disease, who applied to the cardiology outpatient clinic for routine control or check-up. Patients with left ventricular ejection fraction (LVEF) <55%, more than mild degree of valvular heart disease, congenital heart disease, rhythm or conduction disorders on electrocardiography (ECG) were excluded from the study.

Blood samples were taken in the morning fasting, mostly the day before echocardiography. In patients undergoing dialysis, blood tests were performed before dialysis. Renal functions were evaluated with the estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for adults in line with the guideline published by the Turkish Public Health Agency.

The study was performed in accordance with the Declaration of Helsinki after having approval of the research protocol from the Local Ethics Committee. Additionally, all participants provided signed detailed written informed consent.

Echocardiographic evaluation

Transthoracic echocardiographic evaluation of all patients was performed with the Epiq 7C ultrasound system (Philips, Andover, MA, USA) using a 2.3-3.5 MHz transducer probe. During the test simultaneous ECG recording was made. Left ventricular wall thicknesses, heart chamber diameters, and LV systolic function

were evaluated from standard parasternal and apical windows, B-mode and M-mode images, according to the current recommendation guidelines of the American Society of Echocardiography [1]. Diastolic function of LV was assessed with pulse wave (PW) Doppler from the trans-mitral velocities and with tissue Doppler imaging (TDI) measurements from the mitral annular region.

Left atrial appendage evaluation was performed from parasternal short axis view using PW Doppler and TDI. The cursor was placed on the apex of the LAA after visualizing LAA and making required adjustments (Figure 1). Then LAA emptying velocity (LAA EV) was measured with PW Doppler (Figure 2), early diastolic (LAA Em), contraction (LAA Am) and systolic (LAA Sm) velocities were measured using TDI (Figure 3) and averaged for five consecutive cardiac cycles.

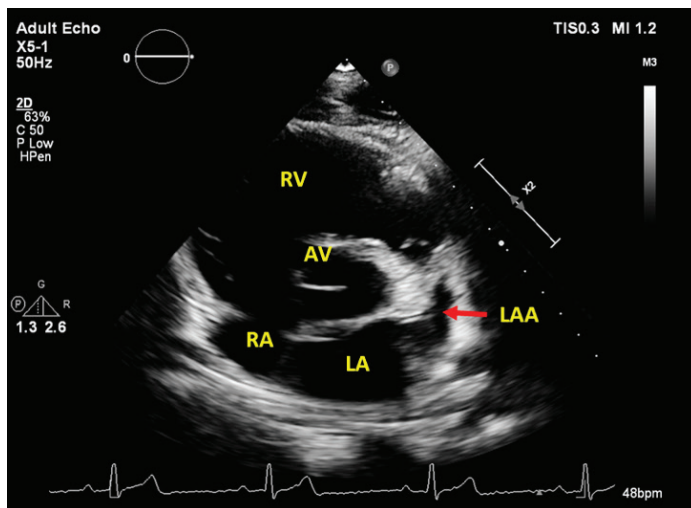


Figure 1. Parasternal short axis view image showing left atrial appendage (LAA) in transthoracic echocardiographic assessment. LA, left atrium; RA, right atrium; RV, right ventricle; AV, aortic valve.

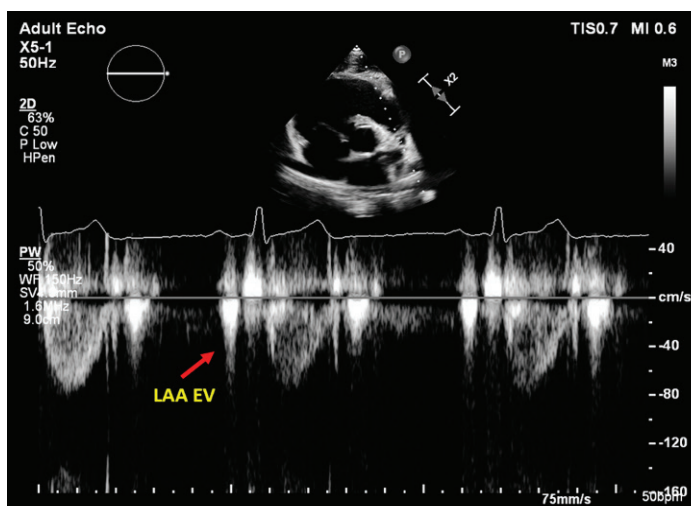


Figure 2. Parasternal short axis view image showing the left atrial appendage emptying velocity (LAA EV) obtained using pulse wave Doppler.

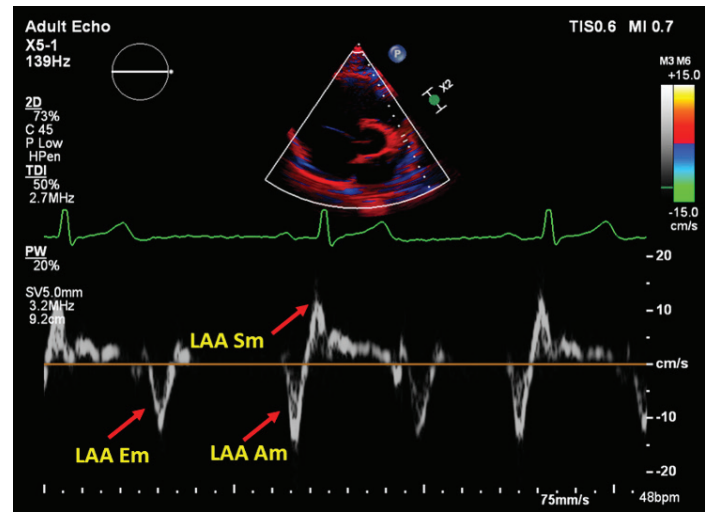


Figure 3. Parasternal short axis view image showing the left atrial appendage early diastolic (LAA Em), contraction (LAA Am) and systolic (LAA Sm) velocities were measured using tissue Doppler imaging.

For LA strain analysis, standard apical two- and four-chamber images were recorded at a speed of 60-100 frames/sec on gray scale for 3 cycles. Offline LA strain analysis was performed using dedicated software (Qlab advanced quantification software version 10.1, Philips Medical Systems, Bothell, WA, USA). After LA endocardial borders were determined manually, the region of interests (ROI) were designated. Atrial peak longitudinal strain (PLS), and peak contraction strain (PCS) reflecting the reservoir function, and the atrial pump function, respectively, were calculated from the strain curves obtained by two-dimensional speckle tracking analysis (2DSTE). Atrial conduit function was calculated by subtracting the PCS value from the PLS value. The QRS onset was taken as a reference point (Figure 4).

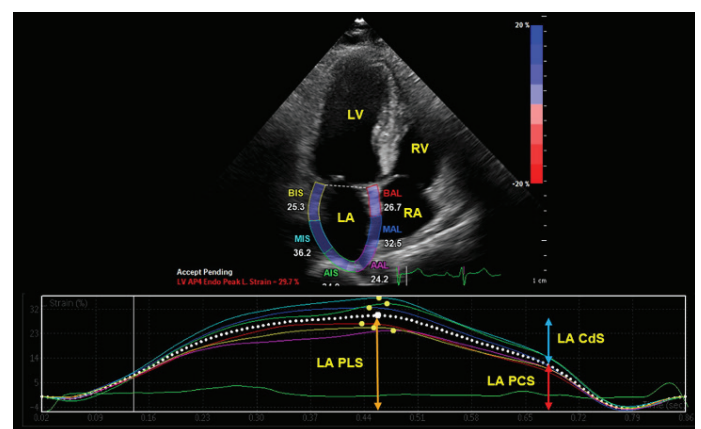


Figure 4. Left atrial strain imaging with two dimensional speckle tracking echocardiography from apical four chamber view of a study patient. Yellow arrow shows peak longitudinal strain (PLS), red arrow shows peak contraction strain (PCS), blue arrow shows conduit strain (CdS).

Statistical Analysis

SPSS 26 program was used to evaluate the data obtained in

the study. The normality of the distribution was determined by the Kolmogorov-Smirnov test. Results were expressed as mean \pm standard deviation. Normally distributed variables were compared with Student's T test, and non-normally distributed variables were compared with Mann Whitney-U test. Chi-square test was used to compare categorical variables. P value less than 0.05 was considered statistically significant. Pearson analysis was used for continuous variables and Spearman test was used for non-continuous variables in the correlation analysis. The correlation coefficient (r) was calculated. Independent determinants of LA PLS and LAA EV parameters were ascertained by multivariate linear regression analysis.

Results

The patient group constituted of 52 subjects with ESRD (mean age, 46.01 \pm 11.08 years; 40.4% female) while there were 60 individuals (mean age, 48.26 \pm 10.63; 53.3% female) in the control group. Age, gender, BSA, history of diabetes mellitus (DM), smoking, hyperlipidemia (HL) and CAD were similar in both groups. Presence of hypertension (HT), use of beta blockers and calcium channel blockers (CCBs), and systolic blood pressure (SBP) were found to be significantly higher in the patient group (Table 1).

Table 1. Evaluation of demographic and clinical characteristics of the study groups

Parameter	Patients group (n=52)	Control group (n=60)	p value
Age	46.01 \pm 11.98	48.08 \pm 10.73	0.338
Female, % (n)	40.4 (21)	53.3 (32)	0.171
SBP (mmHg)	125.76 \pm 14.15	118.51 \pm 15.38	0.011
DBP (mmHg)	76.25 \pm 7.40	74.08 \pm 9.18	0.176
Heart rate (beat/m)	73.23 \pm 10.65	72.45 \pm 10.07	0.691
BSA (m ²)	1.85 \pm 0.24	1.86 \pm 0.19	0.770
Hypertension, % (n)	78.8 (41)	23.3 (14)	<0.001
Hyperlipidemia, % (n)	26.9 (14)	20 (12)	0.387
Diabetes mellitus, % (n)	21.2 (11)	11.7 (7)	0.173
Smoking, % (n)	23.1 (11)	10 (6)	0.06
CAD, % (n)	11.5 (6)	5 (3)	0.204
ACEI /ARB, % (n)	19.2 (10)	12.2 (6)	0.315
Beta blockers, % (n)	38.5 (20)	10 (6)	<0.001
CCB, % (n)	69.2 (36)	6.7 (4)	<0.001
Diuretics, % (n)	3.8 (2)	3.3 (2)	0.884
Statin % (n)	23.1 (12)	11.7 (7)	0.109
Dialysis % (n)	50 (26)	-	

SBP, systolic blood pressure; bpm, beat per minute DBP, diastolic blood pressure; BSA, body surface area; CAD, coronary artery disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blockers.

Half of ESRD patients (n=26) were on dialysis. The mean dialysis time was 15.19 \pm 23.82 months (min 1 month, maximum 108 months). Patients undergoing dialysis did not differ significantly from non-dialysis patients in terms of demographic and echocardiographic characteristics.

In the echocardiographic evaluation, left ventricular wall thickness and diameters of all heart chambers were significantly higher in the patient group. Although EF was normal in both groups, it was found to be significantly lower in the patient group. In addition, E/e' ratio, which is a sensitive indicator of diastolic function, and systolic pulmonary artery pressure were significantly higher in the patient group compared to the control group. When the left atrium size and functions are examined, ESRD patients had significantly increased LAV and LAVI values compared to controls. Demonstrating left atrial appendage functions and left atrial strain assessment, LAA EV, Am and Sm values and LA PLS, PCS, CdS measurements were found to be significantly lower in the patient group (Table 2).

Table 2. Laboratory findings of the study groups

Parameter	Patients group (n=52)	Control group (n=60)	p value
Glucose (mg/dl)	103.67 \pm 31.48	100.11 \pm 18.96	0.467
Creatinine (mg/dl)	6.61 \pm 1.79	0.92 \pm 0.81	<0.001
eGFR (ml/min/1.73m ²)	8.82 \pm 3.25	101.50 \pm 17.56	<0.001
Sodium (mmol/L)	138.63 \pm 4.51	141 \pm 2.29	0.001
Potassium (mmol/L)	5.25 \pm 0.66	4.40 \pm 0.30	<0.001
Uric aside (mg/dl)	7.99 \pm 1.78	4.86 \pm 1.27	<0.001
Total cholesterol (mg/dl)	202.52 \pm 43.82	207.15 \pm 34.84	0.543
LDL (mg/dl)	130.19 \pm 34.67	136.10 \pm 31.59	0.356
HDL (mg/dl)	43.01 \pm 12.48	52.40 \pm 15.02	0.01
Triglycerides (mg/dl)	170.29 \pm 82.53	131.54 \pm 75.55	0.012

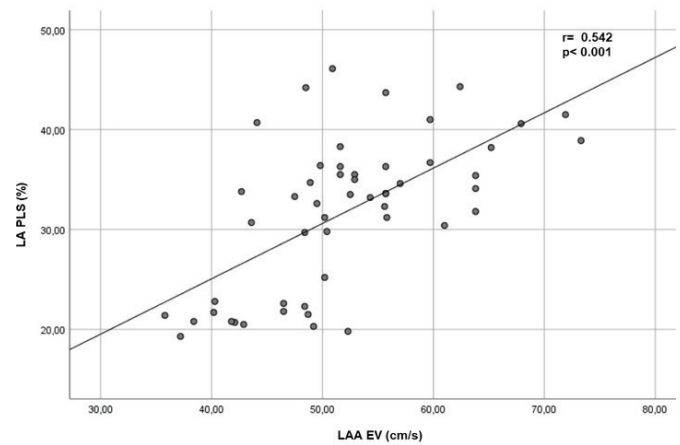
eGFR, estimated glomerular filtration rate; LDL, low density lipoprotein; HDL, high density lipoprotein.

In correlation analyzes performed in ESRD patients LAA EV did not showed significant correlation with demographic characteristics, risk factors, and laboratory findings except for uric acid (r= -0.387, p=0.006). LAA EV measurements showed a strong positive correlation with LAVI, LA PLS (Figure 5), and LA PCS values, and a negative correlation with LV diameters, and E/e' value. While LA PLS was negatively correlated with the presence of HT, and DM, and uric acid levels (r= -0.315, p= 0.023; r= -0.282, p= 0.043; r= -0.429, p= 0.02, respectively) there was no significant correlation with other baseline clinical features and laboratory findings. Besides a significant negative correlation was observed between LA PLS and LV wall thickness and diameters, LA diameter, volume, volume index, and E/e' measurements. Table 4 demonstrates the echocardiographic parameters that were significantly associated with the parameters showing LAA and LA functions.

Table 3. Comparison of echocardiographic measurements of the groups

Parameter	Patients group (n=52)	Control group (n=60)	p value
IVS (cm)	1.07±0.16	0.93±0.10	<0.001
PW (cm)	1.05±0.14	0.92±0.10	<0.001
LVEDD (cm)	4.91±0.46	4.64±0.37	0.001
LVESD (cm)	3.26±0.41	2.99±0.26	<0.001
LV EF (%)	59.30±2	60.81±1.50	<0.001
LA (cm)	3.91±0.35	3.64±0.22	<0.001
RA (cm)	3.69±0.34	3.50±0.21	0.001
RV (cm)	3.44±0.28	3.31±0.23	0.012
sPAP (mmHg)	26.73±4.71	23.58±3.61	<0.001
E wave velocity (cm/s)	83.84 ±19.73	78.85 ±15.52	0.139
A wave velocity (cm/s)	81.86±15.04	69.86±14.10	<0.001
E/A ratio	1.06±0.27	1.14±0.23	0.094
DT (msn)	195.29±35.99	182.33±23.73	0.025
IVRT (msn)	96.11±14.85	92.33±11.17	0.123
E'wave velocity (cm/s)	12.80±3.38	13.92±3.45	0.092
E/E' ratio	6.94±2.19	5.81±1.10	0.001
LAV (ml)	59.57±20.12	41.72±10.49	<0.001
LAVI (ml/m ²)	31.81±8.82	22.28±4.89	<0.001
LAA EV (cm/s)	52.36±8.87	67.80±7.35	<0.001
LAA Em (cm/s)	9.15±1.78	11.38±1.94	<0.001
LAA Am (cm/s)	15.38±2.87	19.55±3.53	<0.001
LAA Sm (cm/s)	10.10±1.64	12.78±1.56	<0.001
LA PLS (%)	31.73±7.61	38.43±5.61	<0.001
LA PCS (%)	13.15±3.90	18.28±3.23	<0.001
LA CdS (%)	18.57±5.76	20.14±4.45	0.039

IVS, interventricular septal thickness; PW, posterior wall thickness; LVEDD, Left ventricular end diastolic diameter; LVESD, Left ventricular end systolic diameter; LV EF, Left ventricular ejection fraction; LAD, left atrial end systolic diameter; RAD, right atrial end systolic diameter; RVD, right ventricular end diastolic diameter; DT, deceleration time; IVRT, isovolumetric relaxation time; LAV, left atrial volume, LAVI, left atrial volume index; LAA EV, left atrial appendage emptying velocity; LAA Am, LA contraction velocity; LAA Sm, systolic velocity; PLS, peak longitudinal strain; PCS, peak contraction strain; CdS, conduit strain.


Figure 5. The correlation analysis graph showing the relationship between the left atrial appendix emptying velocity and left atrial peak longitudinal strain.

The study group was also evaluated according to the lowest expected LA PLS value (23%) determined in the multi-center studies [,]. LA PLS was <23% in 14 patients (26.9%) in the ESRD group and 4 subjects (6.7%) in the control group (p=0.004). In the patients group, 14 patients with LA PLS <23% and 38 patients with LA PLS ≥ 23% were compared in terms of demographics, clinical features and laboratory findings. Demographic and clinical characteristics of the two groups were similar except for the BSA. There was no significant difference between risk factors and biochemistry parameters. In echocardiographic evaluation, LV wall thickness and diameters, LA dimensions, E/e, and sPAP values were significantly higher in the group with PLS<23%, while LAA EV and LAA Am values were significantly lower (Table 5).

In the multivariate regression analysis LA PLS and LAVI were found to be independent factors for LAA EV. No significant independent relationship was detected between LA PLS and LAVI, E/e' and uric acid (Table 6). In different multivariate regression analysis models including IVS, PW, LVEDD, LVESD, no different independent significant variables were found for LAA EV and LA PLS.

Table 4. Correlation analysis of left atrial and left atrial appendage functions in the patients group.

	LAA PLS	LAA PCS	IVS	PW	LVEDD	LVESD	LAVI	E/e'
LAA EV	0.542**	0.498**	-0.266	-0.228	-0.307*	-0.329*	-0.499**	-0.314*
LAA Am	0.558**	0.554**	-0.245	-0.234	-0.0407**	-0.432**	-0.289*	-0.246
LA PLS	-	-0.673**	-0.366**	-0.377**	-0.450**	-0.461**	-0.319*	-0.377*
LA PCS	0.673**	-	-0.227	0.0212	-0.303*	-0.298*	-0.282*	-0.231

LAA EV, left atrial appendage emptying velocity; LAA Am, LA contraction velocity; LAA Sm, systolic velocity; PLS, peak longitudinal strain; PCS, peak contraction strain; IVS, interventricular septal thickness; PW, posterior wall thickness; LVEDD, Left ventricular end diastolic diameter; LVESD, Left ventricular end systolic diameter; LAVI, left atrial volume index. *p<0.05, **p<0.01

Table 5. Echocardiographic features of the groups according to LA PLS value.

Parameter	LA PLS <23% (n=14)	LAP PLS ≥ 23% (n=38)	p value
IVS (cm)	1.20±0.16	1.02±0.13	<0.001
PW (cm)	1.17±0.15	1.02±0.13	<0.001
LVEDD (cm)	5.29±0.34	4.77±0.41	0.001
LVESD (cm)	3.59±0.32	3.14±0.38	<0.001
LV EF (%)	58.85±2.34	59.47±1.87	0.330
LA (cm)	4.22±0.41	3.80±0.25	<0.001
sPAP (mmHg)	29.07±5.18	25.86±4.28	0.028
E/E' ratio	8.11±2.70	6.48±1.80	0.017
LAV (ml)	71.87±23.57	55.04±16.88	0.006
LAVI (ml/m ²)	36.27±10.41	30.16±7.67	0.026
LAA EV (cm/s)	49.97±11.20	54.35±7.03	0.007
LAA Em (cm/s)	8.43±1.80	9.41±1.72	0.078
LAA Am (cm/s)	13.13±2.44	16.21±2.58	<0.001
LAA Sm (cm/s)	10.77±1.96	11.07±1.53	0.565

IVS, interventricular septal thickness; PW, posterior wall thickness; LVEDD, Left ventricular end diastolic diameter; LVESD, Left ventricular end systolic diameter; LV EF, Left ventricular ejection fraction; LAD, left atrial end systolic diameter; RAD, right atrial end systolic diameter; RVD, right ventricular end diastolic diameter; DT, deceleration time; IVRT, isovolumetric relaxation time; LAV, left atrial volume, LAVI, left atrial volume index; LAA EV, left atrial appendage emptying velocity; LAA Am, LA contraction velocity; LAA Sm, systolic velocity.

Table 6. Univariate and multivariate linear regression analysis for left atrium and left atrial appendage function parameters in patients group

Variables	Univariate analysis		Multivariate analysis	
	Beta coefficient	p value	Beta coefficient	p value
LAVI	-0.499	<0.001	-0.352	0.005
LA PLS	0.542	<0.001	0.365	0.008
E/e'	-0.314	0.026	-0.052	0.670
Uric aside	-0.387	0.006	-0.194	0.118

Variables	Univariate analysis		Multivariate analysis	
	Beta coefficient	p value	Beta coefficient	p value
LAVI	-0.319	0.021	-0.030	0.833
LAA EV	0.542	<0.001	0.413	0.008
E/e'	-0.377	0.007	-0.174	0.175
Uric aside	-0.429	0.02	-0.243	0.065

LAA EV, left atrial appendage emptying velocity; LAVI, left atrial volume index; LA PLS, left atrial peak longitudinal strain.

Discussion

In the present study, LAA functions in patients with ESRD with sinus rhythm, candidates for transplantation were examined with TTE for the first time to the best of our knowledge. LAA EV value were found to be significantly lower in the patients group than in the control group. Left atrial functions were evaluated using 2D

strain analysis, significantly decreased LA strain values were found in the patients group. Additionally, regression analysis revealed that LA PLS and LAVI were independent markers for LAA EV.

Evaluation of LA functions is of great importance in predicting the prognosis and development of CV events in CKD patients []. Ayer et al. showed that the LA reservoir and conduit strain were independently associated with major adverse cardiovascular events at 2-year follow-up in ESRD patients []. Left atrial functions are affected by various mechanisms in patients with renal failure such as CV risk factors, volume overload, chronic inflammation, neurohumoral changes and increased oxidative stress [,]. In our study, high HT rate, high SBP levels, and volume overload may explain the increased LV wall thickness, and diameters of heart chambers, diastolic dysfunction, and the resulting decrease in LA functions compared to the control group. LA strain assessment with 2DSTE is a sensitive, reliable and less load dependent method that can show the deterioration of LA functions earlier []. Ohara et al. investigated the LA strain with 2DSTE in CKD patients with normal left atrial size and found a significant decrease in LA reservoir strain compared to the control group. These findings were interpreted in favor of subclinical deterioration in LA functions before the change in atrial volume in CKD patients []. Our study was conducted in patients with ESRD patients, and significant structural cardiac changes were observed compared to the control group. Although LA PLS was significantly correlated with LV wall thickness, and diameters, and LAVI in the patients group, they were not found to be independent predictors of LA PLS. These findings may support that apart from overt structural changes, atrial fibrosis associated with uremic toxins, increased renin-angiotensin system activity and chronic inflammation may affect LA functions.

Cardiovascular risk factors, atherosclerosis, hypercoagulability, cardiac structural and functional changes, and atrial arrhythmias are among the causes of increased stroke risk in patients with CKD. Studies have shown that CKD is an independent factor for the structural and functional changes in the left atrium [,], and atrial mechanical changes and remodeling contribute to the development of ischemic stroke independent of CV risk factors and AF [, ,]. In general population, 15-30% of all ischemic cerebral infarcts are considered to be of cardiac origin [,] and in approximately 90% of cardio-embolic events, the thrombus originates from LAA []. In a study by Handke et al. in stroke patients, it was shown that the LAA EV value measured by TEE, regardless of rhythm, is an important determinant of thromboembolism, and that it significantly predicts the development of thrombus and SEC at a value of <55 cm/s []. Karabay et al. demonstrated that LA strain parameters predicted

LAA functions in patients who had cardioembolic stroke in sinus rhythm []. In our study, a significant relation was observed between LAA EV and LA PLS in ESRD patients with sinus rhythm. Additionally, regression analysis revealed that LA PLS and LAVI were independent markers for LAA EV. Supporting these findings, LAA flow rates were found to be significantly lower in patients with LA PLS < 23% in the patients group.

Another important finding in our study is the significant correlation between blood uric acid level and LAA EV and LA PLS values. Çelik et al. demonstrated that increased uric acid levels were associated with decreased LAA peak flow velocity in AF patients []. Proposed mechanism for this relationship is that increased uric acid levels may cause atrial fibrosis and remodeling associated with chronic inflammation and increased oxidative stress.

It has been shown that the risk of stroke and AF is higher in ESRD patients who are on hemodialysis [,]. In a study by Yıldırım et al., it was shown that left atrial deformation parameters were better in transplant patients than in hemodialysis patients []. In our study, the basic clinical and echocardiographic features of hemodialysis patients did not differ significantly compared to patients who did not undergo hemodialysis. Although half of the patients were dialysis patients, it was thought that this might be related to the short average dialysis times.

In conclusion, decreased LAA mechanical functions was observed in relation to LA volume and functions in patients with ESRD who were planned for transplantation in sinus rhythm. These findings may suggest that evaluation of LAA functions may be helpful in detecting CKD patients at increased risk of developing atrial arrhythmias and stroke. Although TEE is the gold standard in investigating LAA functions, it will not be routinely applied, and it is difficult to tolerate in patients with ESRD, especially in dialysis patients. TTE is a readily applicable test in clinical practice and follow-ups in these patients. Supporting the current findings with larger studies may change the follow-up and treatment approaches in these patients.

Limitations of the study

The main limitation of the study is that it was conducted on a small sample. Functions of LAA was evaluated with only TTE, TEE was not performed. We did not perform ambulatory rhythm monitoring for paroxysmal AF detection. Since it was an observational study, development of AF or cerebrovascular event (CVE) was not investigated in the follow-up of the patients and whether our findings predicted these events. Additionally, the QLAB software system developed for LV strain analysis were used for left atrial strain analysis. Several studies have shown that the QLAB software system is reliable and has good reproducibility for atrial strain analysis [,].

Declaration of conflict of interest

Each author has contributed, read, and approved the manuscript; and none of the authors has any conflict of interest, financial or otherwise.

Conflict of interest

The study did not get any type of financial support. The authors declared no conflict of interest.

References

1. Stevens PE, O'Donoghue DJ, de Lusignan S, et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. *Kidney Int.* 2007; 72:92–99. doi: 10.1038/sj.ki.5002273.
2. Thompson S, James M, Wiebe N, et al. Alberta Kidney Disease Network. Cause of death in patients with reduced kidney function. *J Am Soc Nephrol.* 2015; 26:2504–2511. doi: 10.1681/ASN.2014070714.
3. Major RW, Cheng MRI, Grant RA, et al. Cardiovascular disease risk factors in chronic kidney disease: a systematic review and meta-analysis. *PLoS One.* 2018;13:e0192895. doi: 10.1371/journal.pone.0192895.
4. Buglioni A, Burnett JC Jr. Pathophysiology and the cardiorenal connection in heart failure. Circulating hormones: biomarkers or mediators. *Clin Chim Acta.* 2015;443:3–8. doi: 10.1016/j.cca.2014.10.027.
5. Nasrallah R, Hassoun R, Hébert RL. PGE2, Kidney Disease, and Cardiovascular Risk: Beyond Hypertension and Diabetes. *J Am Soc Nephrol.* 2016;27:666–676. doi: 10.1681/ASN.2015050528.
6. Alhaj E, Alhaj N, Rahman I, Niazi TO, Berkowitz R, Klapholz M. Uremic cardiomyopathy: an underdiagnosed disease. *Congest Heart Fail.* 2013;19:E40–E45. doi: 10.1111/chf.12030.
7. Di Lullo L, Gorini A, Russo D, Santoboni A, Ronco C. Left ventricular hypertrophy in chronic kidney disease patients: from pathophysiology to treatment. *Cardiorenal Med.* 2015;5:254–266. doi: 10.1159/000435838.
8. Little WC. Heart failure with a normal left ventricular ejection fraction: diastolic heart failure. *Trans Am Clin Climatol Assoc.* 2008;119:93–99.
9. Dad T, Weiner DE. Stroke and chronic kidney disease: epidemiology, pathogenesis, and management across kidney disease stages. *Semin Nephrol.* 2015 Jul;35(4):311–22. doi: 10.1016/j.semnephrol.2015.06.003.
10. Savelieva I, Bajpai A, Camm AJ. Stroke in atrial fibrillation: update on pathophysiology, new antithrombotic therapies, and evolution of procedures and devices. *Ann Med* 2007;39:371e391. doi: 10.1080/07853890701320662.



11. Wong JM, Welles CC, Azarbal F, Whooley MA, Schiller NB, Turakhia MP. Relation of left atrial dysfunction to ischemic stroke in patients with coronary heart disease (from the heart and soul study). *Am J Cardiol.* 2014 May 15;113(10):1679-84. doi: 10.1016/j.amjcard.2014.02.021.
12. Stoddard MF, Dawkins PR, Prince CR, Ammash NM. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: A transesophageal echocardiographic study. *J Am Coll Cardiol.* 1995; 25:452–459. doi: 10.1016/0735-1097(94)00396-8.
13. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg.* 1996; 61:755–759. doi: 10.1016/0003-4975(95)00887-X.
14. Nakanishi K, Jin Z, Russo C, et al. Association of chronic kidney disease with impaired left atrial reservoir function: A community-based cohort study *Eur J Prev Cardiol.* 2017 Mar;24(4):392-398. doi: 10.1177/2047487316679903.
15. Sun Y, Ramires FJ, Weber KT. Fibrosis of atria and great vessels in response to angiotensin II or aldosterone infusion. *Cardiovas Res* 1997; 35: 138–147. doi: 10.1016/s0008-6363(97)00097-7.
16. Ghoshal S, Freedman BI. Mechanisms of Stroke in Patients with Chronic Kidney Disease. *Am J Nephrol.* 2019;50(4):229-239. doi: 10.1159/000502446.
17. Lee RJ, Bartzokis T, Yeoh TK, et al. Enhanced detection of intracardiac sources of cerebral emboli by transesophageal echocardiography. *Stroke* 1991; 22:734–9. doi: 10.1161/01.str.22.6.734.
18. Omran H, Jung W, Rabahieh R, et al. Imaging of thrombi and assessment of left atrial appendage function: a prospective study comparing transthoracic and transoesophageal echocardiography. *Heart.* 1999 Feb;81(2):192-8. doi: 10.1136/hrt.81.2.192.
19. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2015;16:233-271. doi: 10.1093/ehjci/jev014.
20. Morris DA, Takeuchi M, Krisper M, et al. Normal values and clinical relevance of left atrial myocardial function analysed by speckle-tracking echocardiography: multicentre study. *Eur Heart J Cardiovasc Imaging.* 2015 Apr;16(4):364-72. doi: 10.1093/ehjci/jeu219. Epub 2014 Nov 3.
21. Nielsen AB, Skaarup KG, Hauser R, et al. Normal values and reference ranges for left atrial strain by speckle-tracking echocardiography: the Copenhagen City Heart Study. *Eur Heart J Cardiovasc Imaging.* 2021 Dec 18; 23(1):42-51. doi: 10.1093/ehjci/jeab201.
22. Gan GCH, Kadappu KK, Bhat A, et al. Left Atrial Strain Is the Best Predictor of Adverse Cardiovascular Outcomes in Patients with Chronic Kidney Disease. *J Am Soc Echocardiogr.* 2021 Feb; 34(2):166-175. doi: 10.1016/j.echo.2020.09.015.
23. Ayer A, Banerjee U, Mills C, et al. Left atrial strain is associated with adverse cardiovascular events in patients with end-stage renal disease: Findings from the Cardiac, Endothelial Function and Arterial Stiffness in ESRD (CERES) study. *Hemodial Int.* 2022 Jul;26(3):323-334. doi: 10.1111/hdi.13008.
24. Rao AK, Djamali A, Korcarz CE, Aeschlimann SE, Wolff MR, Stein JH. Left atrial volume is associated with inflammation and atherosclerosis in patients with kidney disease. *Echocardiography.* 2008;25:264–269. doi: 10.1111/j.1540-8175.2007.00589.x.
25. Ravarotto V, Bertoldi G, Innico G, Gobbi L, Calò LA. The Pivotal Role of Oxidative Stress in the Pathophysiology of Cardiovascular-Renal Remodeling in Kidney Disease Antioxidants (Basel). 2021 Jun 29; 10(7):1041. doi: 10.3390/antiox10071041.
26. Yuda, S. Current clinical applications of speckle tracking echocardiography for assessment of left atrial function. *J. Echocardiogr.* 2021, 19, 129–140. doi: 10.1007/s12574-021-00519-8.
27. Ohara Y, Yoshimura Y, Fukuoka Y, et al. Early detection of left atrial strain abnormalities by speckle-tracking in patients with chronic kidney disease and normal left atrial size. *J Am Soc Echocardiogr.* 2011;24: 898–908. doi: 10.1016/j.echo.2011.04.014.
28. Kadappu KK, Abhayaratna K, Boyd A, et al Independent echocardiographic markers of cardiovascular involvement in chronic kidney disease: the value of left atrial function and volume. *J Am Soc Echocardiogr.* 2016;29:359–367. doi: 10.1016/j.echo.2015.11.019.
29. Kadappu KK, Kuncoro AS, Hee L, et al. Chronic kidney disease is independently associated with alterations in left atrial function. *Echocardiography.* 2014;31:956–964. doi: 10.1111/echo.12503.
30. Habibi M, Zareian M, Ambale Venkatesh B, et al. Left Atrial Mechanical Function and Incident Ischemic Cerebrovascular Events Independent of AF: Insights From the MESA Study *JACC Cardiovasc Imaging.* 2019 Dec;12(12):2417-2427. doi: 10.1016/j.jcmg.2019.02.021.
31. Leong DP, Joyce E, Debonnaire P, et al. Left atrial dysfunction in the pathogenesis of cryptogenic stroke: novel insights from speckle-tracking echocardiography. *J Am Soc Echocardiogr* 2017;30:71–9. doi: 10.1016/j.echo.2016.09.013.
32. Sanchis L, Montserrat S, Obach V, et al. Left atrial function is impaired in some patients with stroke of undetermined etiology: potential implications for evaluation and therapy. *Rev Esp Cardiol (Engl Ed)* 2016;69:650–6. doi: 10.1016/j.rec.2015.11.033.
33. Ferro JM. Cardioembolic stroke: an update. *Lancet Neurol.* 2003;2:177–88. doi: 10.1016/s1474-4422(03)00324-7.

34. Di Tullio MR, Homma S. Mechanisms of cardioembolic stroke. *Curr Cardiol Rep.* 2002;4:141–8. doi: 10.1007/s11886-002-0027-3.
35. Yaghi S, Song C, Gray WA, Furie KL, Elkind MS, Kamel H. Left atrial appendage function and stroke risk. *Stroke* 46, 3554–3559. doi: 10.1161/STROKEAHA.115.011273.
36. Handke M, Harloff A, Hetzel A, Olschewski M, Bode C, Geibel A. Left atrial appendage flow velocity as a quantitative surrogate parameter for thromboembolic risk: determinants and relationship to spontaneous echocontrast and thrombus formation—a transesophageal echocardiographic study in 500 patients with cerebral ischemia. *J Am Soc Echocardiogr.* 2005 Dec;18(12):1366–72. doi: 10.1016/j.echo.2005.05.006.
37. Karabay CY, Zehir R, Güler A, et al. Left atrial deformation parameters predict left atrial appendage function and thrombus in patients in sinus rhythm with suspected cardioembolic stroke: a speckle tracking and transesophageal echocardiography study. *Echocardiography.* 2013 May;30(5):572-81. doi: 10.1111/echo.12089. Epub 2013 Jan 11.
38. Bo S, Gambino R, Durazzo M, et al. Associations between serum uric acid and adipokines, markers of inflammation, and endothelial dysfunction. *J Endocrinol Invest* 2008; 31: 499–504. doi: 10.1007/BF03346397.
39. Power A, Chan K, Singh SK, Taube D, Duncan N. Appraising stroke risk in maintenance hemodialysis patients: A large single-center cohort study. *Am J Kidney Dis* 2012;59:249-57. doi: 10.1053/j.ajkd.2011.07.016.
40. Korantzopoulos, P.G., Goudevenos, J.A. Atrial fibrillation in end-stage renal disease: An emerging problem. *Kidney Int.* 2009 Aug;76(3):247-9. doi: 10.1038/ki.2009.144.
41. Yildirim U, Akcay M, Coksevim M, Turkmen E, Gulel O. Comparison of left atrial deformation parameters between renal transplant and hemodialysis patients. *Cardiovasc Ultrasound.* 2022 Feb 25;20(1):5. doi: 10.1186/s12947-022-00275-4.
42. Vianna-Pinton R, Moreno CA, Baxter CM, Lee KS, Tsang TS, Appleton CP. Two-dimensional speckle-tracking echocardiography of the left atrium: feasibility and regional contraction and relaxation differences in normal subjects. *J Am Soc Echocardiog.* 2009 Mar; 22(3):299-305. doi: 10.1016/j.echo.2008.12.017.
43. Cameli M, Caputo M, Mondillo S, et al. Feasibility and reference values of left atrial longitudinal strain imaging by two dimensional speckle tracking. *Cardiovasc Ultrasoun.* 2009 Feb 8; 7:6. doi: 10.1136/hrt.81.2.192.