



# Left Atrial Function and Volume as Independent Markers of Cardiovascular Involvement in Early Chronic Kidney Disease

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## Abstract

**Aim:** value of left atrium (LA) volume and function evaluated by strain analysis in the detection of myocardial involvement in early chronic kidney disease (CKD) patients with coexistent of hypertension.

**Methods:** 33 patients with CKD stage 2 or stage 3, with mild hypertension compared with 32 age matched hypertensive patients with normal kidney function and 30 healthy control subjects, all participants underwent trans thoracic echocardiography to assess left ventricular (LV) systolic and diastolic function, LV mass and LA volume index (LAVI) by 2D and pulsed wave Doppler imaging, and LA segmental strain measured by tissue Doppler imaging (TDI).

**Results:** Stage 3 CKD had the most reduced diastolic function compared with other groups. (LAVI) was higher significantly in both CKD group (36.2±8.4 ml/m<sup>2</sup>) and HT group (34.31±4.75 ml/m<sup>2</sup>) compared to control group (22.18±3 ml/m<sup>2</sup>) (p=0.001), LAVI was significantly higher in stage 3 compared with stage 2 CKD (p=0.001), Global systolic strain (GS) was significantly reduced in CKD group (17.48±4.3%) compared to both HT group (27.92±5.17%) and controls (31.75±6.8%) (p=0.001), GS was significantly lower in HT group compared with controls (p=0.014), systolic strain of four left atrial walls were different significantly between CKD group and both HT and control groups. there was high significant difference between stage 2 and stage 3 CKD as regard left atrial lateral and anterior walls systolic strain (p=0.001), inferior and septal wall systolic strain were significantly lower in stage 3 compared to stage 2 CKD.

**Conclusion:** LA dysfunction and enlargement are evident in patients with early CKD, LA systolic strain was reduced in CKD earlier than LA enlargement which occur later, hence LA systolic strain and volume index could be used to detect myocardial involvement in early CKD.

**Keywords:** CKD; LA function; LAVI; Strain imaging

Abbreviations: LA: Left Atrium; CKD: Chronic Kidney Disease; LV: Left Ventricular; LAVI: Left Atrium Volume Index; TDI: Tissue Doppler Imaging; HT: Hypertensive; GFR: Glomerular Filtration Rate; CVD: Cardiovascular Disease; ESRD: End Stage Renal Disease; RAAS: Renin-Angiotensin-Aldosterone System; S: Systolic Strain; SPSS: Statistical Program for Social

Science; SD: Standard Deviation; ANOVA: A One-Way Analysis Of Variance; LVMI: Left Ventricular Mass Index; BMI: Body Mass Index; LVEF: Left Ventricular Ejection Fraction; GS: Global Systolic Strain; ACE: Angiotensin Converting Enzyme

## Introduction

Chronic kidney disease (CKD) includes either glomerular filtration rate (GFR)  $\leq$  60 ml/min/1.73 m for more than 3 months, or other pathological abnormalities or markers of kidney damage [1].

Cardiovascular mortality and morbidities are high in CKD, and the cardiovascular disease (CVD) outcomes worsens in the presence of CKD [2,3] both CKD and CVD share the common traditional risk factors. The traditional (Framingham risk score) underestimate cardiovascular risk in patients with CKD [4], hence a need for non-invasive cardiac markers to predict future adverse cardiac events in CKD patients.

The modified national kidney foundation classification for CKD [5] all stages have high risk for adverse CVD, however  $\geq$  11% risk for adverse cardiovascular events reported in stage 3 CKD [6].

The left atrium (LA) has multiple functions, during ventricular systole diastole [7].

LA enlargement and changes in LA volume has been reported to predict cardiovascular event in dialysis patients [8], however hypertrophy of left ventricle and systolic dysfunction in end stage renal disease (ESRD) may alter LA size and function.

There are limited data regarding LA involvement in early CKD, hypertension and diabetes mellitus commonly present with CKD, both of them may alter LA function and volume independently [9,10]. Activation of renin-angiotensin-aldosterone system (RAAS) in CKD caused atrial fibrosis [11,12] which leads to LA enlargement and dysfunction. Evaluation of LA function by conventional echocardiography is challenging, strain imaging is semi-automated technique and an angle-independent may provide a simple, quantitative assessment of atrial function [13].

The present study investigates the value of LA volume and function evaluated by strain analysis in the detection of myocardial involvement in early CKD patients with coexistent of hypertension.

## Patients and Methods

The study was performed at cardiovascular department at Tanta University Hospital in the period from May 2016 to June 2017. **95 subjects had been included in the study divided into three groups.**

**Group 1:** which include 33 patients with CKD stage 2 or stage 3, 15 stage 2 (eGFR 60-89 ml/min per 1.73 m) and 18 stage 3 (eGFR 30-59 ml/min per 1.73 m<sup>2</sup> by the modified diet in renal disease formula) with mild hypertension on one or more antihypertensive medication, patients were identified from the renal outpatient department.

CKD staging was done according to standard criteria [5] the cause of CKD was hypertension (25), chronic glomerulonephritis (3), polycystic kidney (1), renal calculus (2), drug induced (1) and systemic lupus erythromatosis (1).

Patients had previous cardiovascular, peripheral vascular or cerebrovascular disease were Excluded, patients with valvular heart disease, and history of atrial fibrillation or congestive heart failure all were excluded from the study.

**Group 2** includes 32 age and gender matched patients with mild hypertension controlled on antihypertensive medication, with normal kidney function and had no other cardiac risk factors, no history of cerebrovascular or peripheral vascular disease.

**Group 3** includes 30 Healthy normal control subjects with same age.

All CKD patients underwent transthoracic echocardiography to assess LV function, mass and valvular abnormality; stress echocardiography was done to rule out occult ischemia.

### Written informed consent was obtained from all participants in this study

**Echocardiography:** Trans thoracic echocardiographic examination was done using vivid 9, General Electric, Horten, Norway with 2.5 MHz frequency transducer, 2D, color and pulsed wave Doppler and tissue Doppler imaging (TDI) were obtained from standard echocardiographic views and according to standard practice [14].

**Left ventricular measurement:** LVEF was measured by M-mode of LV walls and internal dimensions in the parasternal long axis view. LV diastolic function pulsed Doppler of Trans mitral flow velocities were obtained with the sample volume placed at the tips of mitral leaflet in the apical four chamber view. Peak E and A velocity, and E/A ratio was calculated, TDI to measure early (E') and late (A') diastolic velocity by placing sample volume at septal and lateral mitral annulus [14,15], E/E' ratio was calculated. LV mass and LV indexed to body surface area was calculated using the LV diameter and wall thickness at end-diastole by M-mode in the parasternal long axis view [16].

**Left atrium measurement:** -LA volume, was obtained using biplane area length method where: LA volume =  $(0.85 \times \text{Area } 4 \text{ ch} \times \text{Area } 2 \text{ ch}) / (\text{Longest LA length})$ . Apical four chamber and two chamber views were used to measure the LA area and long axis at end of ventricular systole LA area was measured by tracing the endocardial border of LA.

While LA long axis dimension was measured as a line perpendicular to the mitral annular plane extending to the back wall of LA. These LA volumes obtained for each subject were indexed to his/her body surface area. BSA was calculated by a simple and commonly used formula "Mosteller formula":  $\text{BSA (m}^2\text{)} = (\text{Height (cm)} \times \text{Weight (kg)} / 3600)^{1/2}$ .

-LA systolic strain, LA systolic strain (S) was measured using color-coded tissue Doppler imaging (TDI) using standard apical views, a sample volume (2 mm because of thin atrial walls) was placed at mid segment of septal and lateral walls of LA (from the apical 4 chamber view), LA inferior and anterior walls (from apical 2 chamber view) and tracked frame by frame to maintain its position within LA wall. Off line analysis was done using available software. Peak systolic strain was measured in each segment and global strain for final analysis was calculated by averaging values from the four LA walls.

### Statistical Analysis

Analysis of data was done using Statistical Program for Social Science (SPSS) version 20.0. Quantitative data were expressed as mean  $\pm$  standard deviation (SD).

The following tests were done: Independent-samples t-test was performed when comparing between two means, a one-way analysis of variance (ANOVA) when comparing between more than two means and Post Hoc test was used for multiple comparisons between different variables.

### Results

95 patients and control subjects were enrolled in this study, patients characteristic: mean age was 59.7 $\pm$ 8 years in CKD group, 58.6 $\pm$ 9 years in hypertensive group and 57.7 $\pm$ 9.1 years in control group with no significant difference between three groups, nineteen patients (57.5%) in CKD group and 18 (56.2%) patients in HT group were male compared with 13 (43.3%) in control group. CKD group and HT group had higher Body mass index (BMI) compared with control group ( $p=0.001$ ) (Table 1) (Figure 1).

		Control (n=33)	CKD (n=30)	HT(n=32)	P1	P2	P3
LVEF (%)	Range	57.2 – 69.4	58.3 – 69.9	58.6 – 68.7	0.107	0.124	0.917
	Mean $\pm$ SD	62.15 $\pm$ 4.62	63.96 $\pm$ 4.12	63.85 $\pm$ 4.14			
LVMI	Range	55.1 – 112.9	66.8 – 127.8	84 – 130	0.001*	0.001*	0.016*
g/m <sup>2</sup>	Mean $\pm$ SD	80.85 $\pm$ 16.8	97.74 $\pm$ 7.56	108.03 $\pm$ 15.11			
LAVI	Range	16.9 – 27.1	25.1 – 47.9	22.4 – 39	0.001*	0.001*	0.147
ml/m <sup>2</sup>	Mean $\pm$ SD	22.48 $\pm$ 3.1	36.82 $\pm$ 8.32	34.31 $\pm$ 4.75			
BMI	Range	24.5 – 31.4	26.6 – 34.7	26.5 – 35	0.001*	0.001*	0.931
Kg/m <sup>2</sup>	Mean $\pm$ SD	28.12 $\pm$ 2.02	30.25 $\pm$ 2.14	30.31 $\pm$ 3.17			

**Table 1:** Comparison between the studied groups regarding LVEF, LVMI, LAVI and BMI  
P1: between control and CKD groups. P2: between control and HT groups, P3: between CKD and HT groups.

## LV Function

LVEF was normal in the studied groups with no significant difference between the three groups. LVMI was significantly high in

both hypertensive and CKD groups compared to controls and significantly higher in HT group (mean  $108.03 \pm 15.1 \text{ g/m}^2$ ) compared to CKD group (mean  $97.74 \pm 17.56 \text{ g/m}^2$ ) ( $p=0.01$ ) (Table 1).

		Control (n=30)	CKD (n=33)	HT(n=32)	P1	P2	P3
A velocity	Range	0.46 – 0.81	0.59 – 0.95	0.48 – 0.86	0.001*	0.451	0.001*
	Mean ± SD	0.63 ± 0.11	0.77 ± 0.11	0.65 ± 0.11			
E/A ratio	Range	0.78 – 1.32	0.61 – 2.14	0.8 – 1.4	0.004*	0.688	0.001*
	Mean ± SD	1.12 ± 0.19	0.86 ± 0.33	1.10 ± 0.2			
E' cm/s	Range	6.38 – 10.8	6.41 – 11.2	6.5 – 9.0	0.001*	0.001*	0.303
	Mean ± SD	9.73 ± 1.02	7.73 ± 1.27	8.0 ± 0.75			
E/E' ratio	Range	6.58 – 8.1	7.49 – 15.56	6.7 – 12	0.001*	0.001*	0.631
	Mean ± SD	7.31 ± 0.40	9.62 ± 2.48	9.36 ± 1.79			

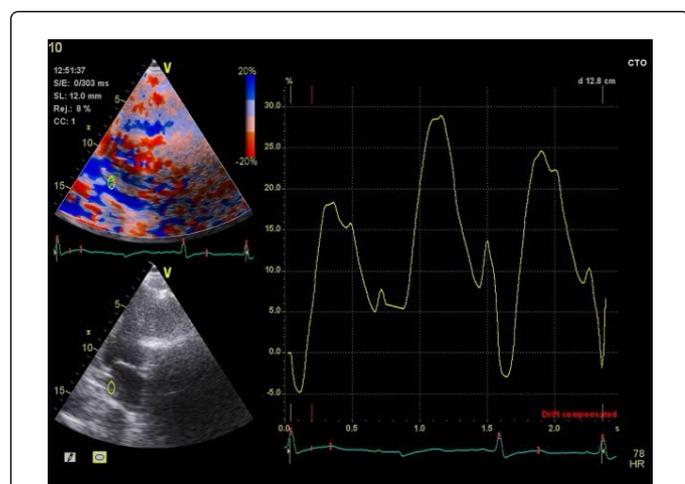
**Table 2:** Comparison between the studied groups regarding diastolic function. P1: between control and CKD groups. P2: between control and HT groups, P3: between CKD and HT groups.

Peak A velocity was significantly higher in the CKD (mean  $0.77 \pm 0.1 \text{ m/s}$ ) compared to both HT (mean  $0.65 \pm 0.1 \text{ m/s}$ ) and controls group ( $p=0.001$ ), there was no significant in E wave velocity between the three groups. E/A ratio was significantly lower in the CKD group compared to HT group ( $p=0.001$ ) and to controls ( $p=0.005$ ). LV diastolic function was reduced in early stages of CKD, in CKD group there were 4 patients (12%) with normal LV diastolic function, 14 patients (42.4%) with grade 1 (impaired relaxation), 12 patients (36.3%) with grade 2 (pseudo normal relaxation) and 3 patients (9%) with grade 3 (restrictive pattern), in contrast, 19% of patients in HT group had normal diastolic function, 46% had impaired relaxation (grade 2), 35% had grade 3 diastolic dysfunction and none had restrictive pattern. Subjects in control group either had normal function or grade 1 of diastolic dysfunction.

and 3 patients with restrictive pattern. E' velocity was significantly lower in the CKD and HT groups compared to controls ( $p=0.001$ ) and E/E' ratio was higher in CKD and HT group compared to controls ( $p=0.001$ ) (Table 2).

## LA Parameters

-LA volume index (LAVI) was significantly larger in both CKD group (mean  $36.82 \pm 8.32 \text{ ml/m}^2$ ) and HT group (mean  $34.31 \pm 4.75 \text{ ml/m}^2$ ) compared to control group (mean  $22.48 \pm 3.1 \text{ ml/m}^2$ ) ( $p=0.001$ ), (Table 1) (Figure 2). Mean LAVI in stage 2 CKD was  $34.50 \pm 5.18 \text{ ml/m}^2$  and in stage 3 CKD was  $45.53 \pm 4.27 \text{ ml/m}^2$ , LAVI was significantly higher in stage 3 compared with stage 2 CKD ( $p=0.001$ ) (Table 3).



**Figure 1:** Systolic strain of LA inferior wall in CKD patient.

Stage 3 CKD had the most reduced diastolic function, 8 patients with impaired relaxation, 7 patients with pseudo normal relaxation



**Figure 2:** LA volume measured by area length method.

	CKD group		P-value
	Stage 2 (n=15)	Stage 3 (n=18)	
<b>LAVI (ml/m<sup>2</sup>)</b>			
<b>Mean ± SD</b>	34.50 ± 5.18	45.53 ± 4.27	<0.001
<b>Range</b>	27.1-39.2	37.2-49.3	

**Table 3:** LAVI compared between the stages of CKD.

### Atrial systolic strain

Global systolic strain (GS) derived as an average of 4 segments (lateral, septal, anterior and inferior walls) was significantly reduced in CKD group (mean 17.48±4.3%) compared to both HT group (mean 27.92±5.17%) and controls (mean 31.75±6.8%) (p=0.001) (Table 4), GS was significantly lower in HT group compared with controls (p=0.014),

systolic strain of four left atrial walls were different significantly between CKD group and both HT and control groups (Table 4) (Figure 1). There was high significant difference between stage 2 and stage 3 CKD as regard left atrial lateral and anterior walls systolic strain (p=0.001), inferior and septal wall systolic strain were significantly lower in stage 3 compared to stage 2 CKD (Table 5).

		Control (n=30)	CKD (n=33)	HT(n=32)	P1	P2	P3
<b>Lateral S (%)</b>	Range	23.22 – 52.23	8.12 – 28.51	20 – 38.5	0.001*	0.001*	0.001*
	Mean ± SD	38.92 ± 9.28	16.31 ± 6.34	28.95 ± 4.85			
<b>Septal S (%)</b>	Range	13.93 – 47.44	7.62 – 20.69	13.5 – 30.8	0.001*	0.002*	0.001*
	Mean ± SD	26.73 ± 9.77	14.35 ± 3.71	20.48 ± 3.98			
<b>Anterior S (%)</b>	Range	17.82 – 47.84	5.83 – 34.78	16.8 – 40.5	0.001*	0.047*	0.001*
	Mean ± SD	32.32 ± 7.87	17.28 ± 8.43	28.51 ± 6.92			
<b>Inferior S (%)</b>	Range	33.92 – 74.74	8.52 – 33.28	30.5 – 64.2	0.001*	0.002*	0.001*
	Mean ± SD	47.51 ± 11.28	19.69 ± 7.61	39.47 ± 8.15			
<b>GS</b>	Range	25.9 – 39.7	12.7 – 23.8	19.5 – 35.5	0.001*	0.014*	0.001*
	Mean ± SD	31.75 ± 6.87	17.48 ± 4.32	27.92 ± 5.17			

**Table 4:** Comparison between the three groups regarding left atrial walls systolic strain and global strain. P1: between control and CKD groups. P2: between control and HT groups, P3: between CKD and HT groups.

	CKD group		P. value
	Stage 2 (n=15)	Stage 3 (n=18)	
<b>Lateral S (%)</b>			
Mean ± SD	15.23 ± 2.92	9.76 ± 1.31	<0.001
Range	11.52-20.52	7.82-11.83	
<b>Septal S (%)</b>			
Mean ±SD	13.25 ± 2.09	11.07 ± 1.92	0.004
Range	11.32-17.24	7.62-13.81	
<b>Anterior S (%)</b>			
Mean ±SD	18.24 ± 7.05	8.65 ± 1.66	0.001
Range	11.62-34.69	5.79-10.63	

Inferior S (%)			
Mean ±SD	18.38 ± 4.50	13.25 ± 4.78	0.005
Range	11.52-22.61	8.49-22.43	

**Table 5:** Comparison between the two stages of CKD group regarding systolic strain of left atrial walls (S%).

## Discussion

Many studies demonstrated increased cardiovascular mortality in ESRD [17,18] patients with stage 4 and 5 CKD (e GFR ≤ 30 ml/min/1.73 m) had increased fluid overload and LV hypertrophy that independently alter LA size and function and leads to abnormalities in traditional echocardiographic parameters. Our study was conducted to detect early cardiac involvement using newer echocardiographic parameters in patients with early stages of CKD. We include patients with stage 2 and 3 CKD with mild hypertension compared to hypertensive patients with same age and normal kidney function and to healthy control subjects, we specifically used a group with HT alone to evaluate the effect of concomitant CKD on LA function, as hypertension independently causes LA changes [18,19].

LVMi was higher significantly in CKD compared to controls this result is agree with the result of Nakanishi et al. [20] our study reported that LVMi was higher in HT group compared with CKD and control groups which is the same results of Kadappu et al. [21].

This study found that LV diastolic function was impaired in early stages of CKD which was the same finding of Takenori et al. [22] who studied left ventricular diastolic dysfunction in the early stages of CKD, compared to 40 non CKD subjects and concluded that impaired diastolic function of LV was observed even in patients with early stages of CKD. LA enlargement in ESRD independent related to LVMi, LVEF and diastolic dysfunction was reported by Tripepi et al. [8,23] they found that "LAVI was an independent predictor of adverse cardiovascular outcomes in patients with ESRD".

Our study found that (LAVI) was larger significantly in early CKD and hypertensive groups compared to controls, with no significant difference between CKD and HT group; (LAVI) could not differentiate between the effects of hypertension alone and hypertension with CKD. Our results were in the same line with the study of Kadappu et al. [21].

However LA systolic strain was reduced significantly in CKD group compared with hypertensive and control groups despite similar (LAVI) in both hypertensive and CKD groups, in the study of Boyd et al. [24] who examine age-related changes at atrial strain measurement in 188 healthy individuals, reported that "atrial strain was altered before volume parameters with aging, strain analysis more sensitive in detecting subclinical atrial dysfunction".

This study found that traditional parameter of left atrial function (peak A velocity) was significantly higher in CKD group compared with other groups, and this represent compensatory increase in late diastolic filling due to the reduction in early diastolic filling and impaired LA compliance with a reduction in reservoir function, these finding was in the same line with the study of Nakanishi et al. [20] who studied the association of CKD with impaired left atrial reservoir function in 69 patients with CKD compared with 289 non CKD subjects, reported that "LA reservoir function was impaired significantly in CKD patients without overt cardiac disease, while LA maximum volume index did not differ between the studied groups".

These results suggest that CKD may alter LA reservoir function before LA enlargement which occurs subsequently as renal dysfunction progress and LA enlargement represent a late marker of LA remodeling.

In our study there was a significant reduction in E' velocity and increase in E/e' ratio in patients of CKD and HT groups compared to controls with no significant difference between HT group and CKD group, hence TDI could not differentiate cardiovascular involvement in CKD patients with HT from those with only HT. Evaluation of global and segmental LA function using systolic strain parameter considered to be a sensitive measure [25,26].

Our study found that LA global strain reduced significantly in CKD group compared to HT and control groups this may be secondary to increased activation of RASS in CKD group which lead to atrial fibrosis and in turn alters LA function and volume, our results demonstrated that LA strain is affected earlier than LA volume in early CKD as left atrial fibrosis would alter LA function (GS) earlier than LA dilatation, which is a more chronic process, these results was the same results of Kadappu et al. [21]. This study demonstrated that alterations in LA function (systolic strain) precede changes in LV function (EF) in patients with CKD and suggest that alterations in LA function may be a predictor of adverse cardiovascular outcomes as reported in previous studies [27,28].

In the study of Kadappu et al. [29] to evaluate LA function and volume in patients with stage 3 CKD compared with patients matched for risk factors and age with normal kidney function and healthy controls, found that LA systolic strain were altered in CKD group, concluded that "LA strain and LAVI may be useful to detect early myocardial involvement in stage 3 CKD" which was the same results of ours.

The presence of CKD had differential effect on LA function and LAVI, thus early monitoring of LA characteristics could be important in patients with CKD to identify which patients require careful monitoring and aggressive medical therapy with ACE inhibitors to improve LA strain parameter and reverse that changes with early treatment as previously reported [30,31].

## Conclusion

Left atrial dysfunction and enlargement are evident in patients with early CKD, LA systolic strain was reduced in CKD earlier than LA enlargement which occur later, hence LA systolic strain and LAVI may be useful to detect myocardial involvement in early CKD and LA strain is more sensitive parameter.

## Ethical standards

This study was approved by the Ethics Committee in the Faculty of Medicine, Tanta University and with ethical standards of Helsinki

Declaration of 1964 and later revision. Written consent was obtained from all patients included in the study.

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This study did not receive any specific grant from funding agencies.

### Conflict of interest

The authors declare that they have no conflict of interest.

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