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To study left atrial volume and left atrial volume index as echocardiographic markers of cardiovascular involvement in patients with chronic kidney disease

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Abstract
Background: Chronic Kidney Disease is a global public health problem and a major risk factor for cardiovascular disease. Hence, it becomes a necessity to identify the predictors of cardiovascular involvement in patients with Chronic Kidney Disease. The present study was done to assess the presence of Left atrial volume (LAV) and Left atrial volume index (LAVi) in patients of CKD stages as markers of cardiovascular involvement.
Materials and Methods: This cross sectional study included sixty patients (n=60) from the randomly selected cases admitted in emergency and indoor medical wards of Guru Nanak Dev Hospital, Amritsar. The sample was divided into three groups of twenty each on the basis of GFR. Group 1 consisted of CKD stage 3 patients, Group 2 consisted of CKD Stage 4 patients and Group 3 consisted of CKD Stage 5 patients. Detailed history, clinical examination and relevant investigations including testing of various biochemical parameters, Electrocardiogram, X-ray Chest PA View and Two Dimensional Transthoracic Echocardiography were done in every patient. Values of Left Atrial Diameter (LAD), Left Atrial Volume (LAV) and Left Atrial volume index (LAVi) were assessed in each of the three groups. Diastolic Dysfunction and values of Ejection Fraction were also assessed in each of the three groups and correlated with Left Atrial Volume Index (LAVi). The data was collected systematically and analysed according to standard statistical methods.
Results: Increased value of LAVi (>34 mL/m^2) was 15% in Group 1, 40% in Group 2, and 65% in Group 3. Increased left atrial volume was significantly related to decreased ejection fraction in CKD stage 4 and 5 ($p<0.05$).
Conclusion: Earlier detection of increased left atrial volume index in CKD patients is imperative as it can further help in deciding the prognosis of the patients.

Keywords: left atrium, chronic kidney disease, left atrial volume, left atrial diameter left atrial volume index

Introduction

Chronic kidney disease (CKD) is an increasingly acknowledged health burden associated with increased morbidity and mortality. The main causes of CKD are based on immunologic reactions (initiated by immune complexes or immune cells), tissue hypoxia and ischemia, exogenous agents like drugs, endogenous substances like glucose or paraproteins, and genetic defects [1]. The global estimated prevalence of CKD is 13.4% [2].

The presence of CKD dramatically increases the risk of adverse outcomes among people with other non communicable diseases. There is a substantial burden of cardiovascular diseases among patients with CKD and end stage renal disease (ESRD). This is supported by evidence that the risk of developing congestive heart failure, atrial fibrillation, coronary artery disease and peripheral artery disease is increased two fold in patients with eGFR <60 mL/min per 1.73m^2 [3-7].

Among the spectrum of cardiovascular diseases in CKD, abnormalities in left ventricular structure and function are common. These often precede the onset of clinical cardiovascular disease in patients with CKD and ESRD. The incidence of left ventricular hypertrophy (LVH) increases with progressive decline in renal function [8]. The left atrium is prone to volume induced changes and hence, which gets profoundly affected in patients with CKD.

Echocardiography is an established non-invasive method for estimating the risk for cardiovascular complications and for guiding treatment of chronic kidney disease patients. Recent guidelines from the American Society of Echocardiography (ASE) have recommended quantification of left atrial size using left atrial volume (LAV) measured by biplane two dimensional (2D) echocardiography. Due to the exquisite sensitivity of LA volume to changes in extracellular fluid volume, the LA has been applied as a non-invasive measure for detecting and monitoring volume overload in clinical studies in CKD patients on dialysis [9].

It is worthwhile to consider left atrium as a reflection of the burden and chronicity of underlying cardiovascular disease. Among the different echocardiographic parameters available for assessing left atrium including diameter, area and volume, the LA

volume has been identified as the most accurate and robust predictor of cardiovascular outcomes. Appropriate indexing of echocardiographic parameters is fundamental in CKD patients. Hence, Left atrial volume index can emerge as a stable marker of cardiovascular involvement in various stages of CKD.

Aim of work

To assess the presence of left atrial volume and left atrial volume index, as parameters of cardiovascular involvement in stages 3, 4 and 5 CKD.

Material and Methods

This cross sectional study included sixty patients (n=60) from the randomly selected cases admitted in emergency and indoor medical wards of Guru Nanak Dev Hospital, Amritsar. This study was undertaken after approval of the Institutional Ethics Committee. Written informed consent was obtained for their inclusion. The sample was divided into three groups of twenty each on the basis of GFR. Group 1 consisted of CKD stage 3 patients (GFR between 30-60 mL/min per 1.73m^2), Group 2 consisted of CKD Stage 4 patients (GFR between 15-29 mL/min per 1.73m^2) and Group 3 consisted of CKD Stage 5 patients (GFR <15 mL/min per 1.73m^2). GFR was calculated using "Cockroft Gault Equation".

Inclusion and Exclusion Criteria

Those patients who fulfilled the criteria for CKD Stage 3, Stage 4 and Stage 5, and having age more than 18 years were included in our study. Patients who aged less than 18 years, had acute kidney injury, malignancies, evidence of major valvular heart disease especially mitral valve disease, previous history of atrial fibrillation were excluded from our study. All patients underwent complete clinical examination including measurement of blood pressure, pulse rate and systemic examination.

Chronic kidney disease (CKD) patients were screened for the following biochemical parameters: Serum Creatinine (Jaffe's method), Blood Urea (Berthelot method), Total Serum Protein, Serum Albumin, RBS, Glycated Haemoglobin, Serum Electrolytes (serum sodium and serum potassium), Complete Urine Examination (spot), CBC, Ultrasound Abdomen, 12 Lead Surface and Resting Electrocardiogram and X-ray Chest PA View (In full inspiration for heart size) and Two dimensional Transthoracic Echocardiography.

Echocardiography procedure and interpretations

Echocardiography was done in all the cases. Two dimensional and two dimensionally guided M-Mode images were recorded from the standardized views. The measurements were done on Philips i E33 Echocardiography machine. Parameters were recorded in accordance with the guidelines by American Society of Echocardiography.

Recommended normal LA diameter is 28-40 mm (2.8-4.0 cm).
Recommended normal LA volume is 22-58 mL.
Recommended upper normal indexed LA volume is 34 mL/m^2.

The echocardiographic measurements included left atrial size, which was assessed by M-Mode measurement of anteroposterior dimension and left atrial volume, which was calculated by using two-dimensional planimetry with Biplanar Simpson's rule on the frame just before the mitral valve opening or planimetry. Left atrial volume index (LAVi) was calculated by the LA Volume to Body surface area ratio. Body surface area was calculated according to DuBois and DuBois's simplified formula ($0.20247*weight^{0.425}*height^{0.725}$) [10].

Values of Left atrial volume and Left atrial volume index were compared among three groups of twenty patients each. Values greater than upper limit of normal were taken as high or increased for Left Atrial Diameter (LAD), Left Atrial Volume (LAV) and Left Atrial volume index (LAVi). Diastolic Dysfunction [11] and values of Ejection Fraction [12] were also assessed in each of the three groups and correlated with Left Atrial Volume Index (LAVi).

Statistical analysis

The data from present study was collected systematically and analysed statistically according to the appropriate standard statistical methods including Chi-Square Test, One-Way ANOVA, Student 't' test (unpaired) and Pearson Correlation coefficient test. Analysis was done using SPSS 19.0 software. 'p' value of less than 0.05 was considered statistically significant.

Results

A total of sixty patients (n=60) with CKD were included in our study after matching our inclusion and exclusion criteria. Gender distribution showed that 25 cases (41.6%) were males and 35 (58.3%) were females. Their age ranged between 30-83 years with mean age 57.71±12.59 years.

Left Atrial Diameter (LAD)

Mean Left Atrial Diameter (LAD) values in different study groups as observed were 4.08±0.77 in Group 1, 4.34±0.70 in Group 2 and 4.34±0.79 in Group 3.There was no significant difference in mean LAD among these groups (p>0.05)(Table 1).

Table 1: Mean value of left atrial diameter in various groups

	No. of Patients	Lad (cm)		'p' value	
		Mean	±SD		
Group-1	20	4.08	0.77	Group 1 v/s Group 2	0.856
Group-2	20	4.34	0.70	Group 2 v/s Group 3	1.000
Group-3	20	4.34	0.79	Group 1 v/s Group 3	1.000

Left Atrial Volume (LAV)

Mean Left Atrial Volume (LAV) values in different study groups as observed were 48.45±8.46 in Group 1, 56.90±7.53 in Group 2 and 59.20±8.05 in Group 3. There was significant difference in mean LAD on comparing group 1 with group 2, and also on comparing group 1 with group 3. (p>0.05) (Table 2).

Table 2: Mean values of left atrial volume in various groups

	No. of Patients	Lav (mL)		'p' value	
		Mean	±SD		
Group-1	20	48.45	8.46	Group 1 v/s Group 2	0.005
Group-2	20	56.90	7.53	Group 2 v/s Group 3	1.000
Group-3	20	59.20	8.05	Group 1 v/s Group 3	0.000

Left Atrial Volume Index (LAVi)

The mean Left Atrial Volume Index (LAVi) values in Group 1,

Group 2 and Group 3 were 27.94±5.86, 34.57±5.24 and 37.00±5.71 respectively. There was significant difference in mean LAVi on inter group comparisons. (p<0.05)(Table 3)

Table 3: Mean values of left atrial volume index in various groups

	No. of Patients	Lavi (mL/m^2)		'p' value	
		Mean	±SD		
Group-1	20	27.94	5.86	Group 1 v/s Group 2	0.001
Group-2	20	34.57	5.24	Group 2 v/s Group 3	0.001
Group-3	20	37.00	5.71	Group 1 v/s Group 3	0.000

LAVi was high in 3 patients (15%), 8 patients (40%) 13 patients (65%) in Group 1, 2 and 3 respectively. A significant difference was only observed in LAVi values on comparing Group 1 with Group 3.(Table 4)

Table 4: Groupwise distribution of patients on the basis of left atrial volume index

LAVi (mL/m^2)	Group-1		Group-2		Group-3		Total
	No. of cases	% age	No. of cases	% age	No. of cases	% age	
Normal (≤34)	17	85	12	60	7	35	36
High (>34)	3	15	8	40	13	65	24
TOTAL	20	100	20	100	20	100	60
'p' value							
Group 1 vs Group 2				0.076			
Group 2 vs Group 3				0.113			
Group 1 vs Group 3				0.001			

Further in our study we found that Diastolic Dysfunction was present in 7 patients (35%) in relation to group 1, 15 patients (75%) in group 2 and in 13 patients (65%) within group 3. This difference was significant on comparing Group 1 with Group 2 and group 3 (p<0.05) respectively.

Correlation analysis

On correlating LAD and diastolic dysfunction we observed that within group 1, Diastolic Dysfunction was present in 3 patients with LAD>4 and 4 patients with had LAD≤4. Similarly in group 2, Diastolic Dysfunction was present in 12 patients with LAD >4 and 3 patients with LAD≤4. In Group 3, 10 patients with LAD>4 and 3 patients with LAD ≤4 showed diastolic dysfunction. The relationship was statistically significant only within group 3 (p<0.05).

For LAVi, Diastolic Dysfunction was present in 2 patients with LAVi>34 and 5 patients with LAVi≤34 within group 1, in 7 patients with LAVi>34 and 8 patients with LAVi ≤34 within group 2 and in 12 patients with LAVi>34 and 1 patient with LAVi≤34 within group 3. The results were statistically significant in relation to only group 3. (p<0.05).

Group wise analysis:

On correlating LAVi in group 1, we observed that LAVi was positively correlated with LAD and the correlation was significant (p<0.05). It was inversely correlated with both GFR and EF but only the decrease in GFR was significantly related to LAVi (p<0.05).

In group 2, LAVi positively correlated with LAD and the correlation was significant (p<0.05). With EF, the correlation was not significant (p>0.05). LAVi was found to be inversely correlated with GFR and the correlation was not significant (p>0.05).

In group 3, LAVi positively correlated with LAD and the correlation was significant (p<0.05). LAVi was inversely correlated with GFR and EF but the correlation was only significant with EF (p<0.05).

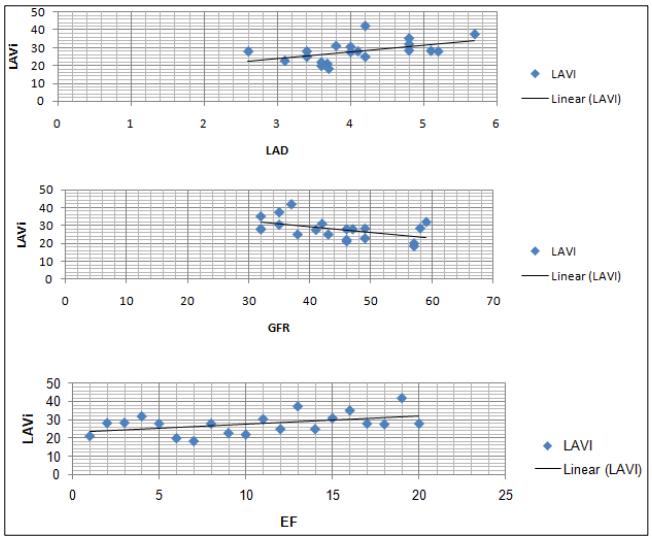

Fig 1: Correlation analysis for group1

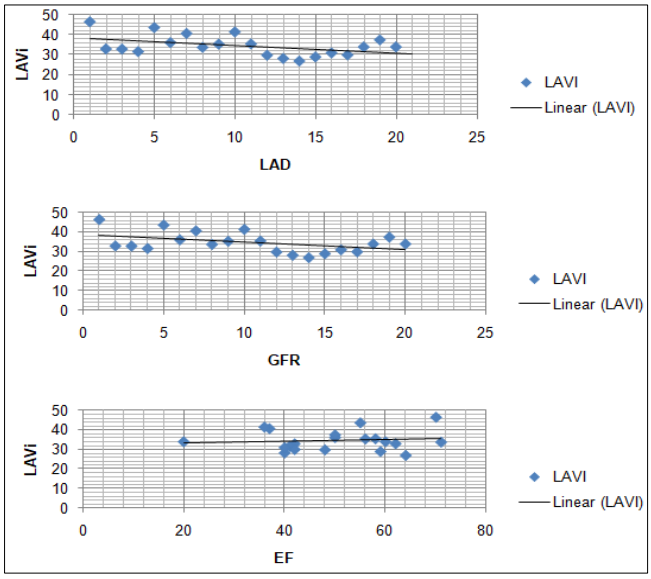

Fig 2: Correlation analysis for group 2

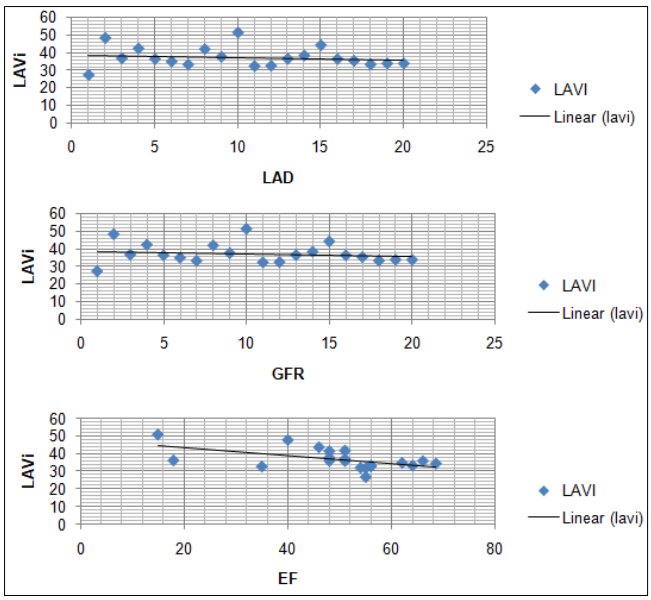

Fig 3: Correlation analysis for group 3

Discussion

The present study shows that with the increase in the stage of CKD, there is an associated increase in LAVi values independent of other echocardiographic parameters. This increase in the value of LAVi has a significant relation with diastolic dysfunction and decreased ejection fraction as the disease progresses from stage 3 to stage 5 CKD.

In the present study, it was observed that the mean age of the patients was 57.71±12.59 years. It was comparable to a previous studies conducted by Cai *et al*, where mean age was 60±10 years in patients with CKD stages 3-5 [13]. Also, it was comparable to the study with that of Kadappu *et al* where mean age was 65.5±16 years [14].

Female population predominated in our study accounted for 58.33%. On contrary, Cai *et al* [13] and Chen *et al* [15] reported male predominance in their studies, with males accounting for 56.1% and 63.9% respectively.

Mean creatinine (mg/dl) observed in our study was 3.01±1.55. In a study by Cai *et al* [13], they reported mean creatinine levels of 2.52±1.39. This difference could be attributed to the difference in the sample size included in both studies.

Mean body surface area (m^2) in our study came out be 1.65±0.17. This was not comparable to previous reports by Kadappu *et al*. [14] and Hee *et al* [16]. These differences could be attributed to the difference in the genetic inbuilt of the population studied.

Various parameters of two dimensional (2D) echocardiography including Left atrial diameter, Left atrial volume, Diastolic dysfunction and Ejection fraction were recorded in accordance with American Society of Echocardiography [14, 17].

The mean value of Left atrial diameter (LAD) (cm) in our study was 4.25±0.75. It was found to be different from the study conducted by Yang *et al* [18], where mean LAD of 3.73±0.63 was present among patients of CKD stages 3-5. Mean LAD of 3.9±0.6 was found in a study by Chen *et al* [15], where patients involving CKD stages 3-5 were included. The differences could be attributed to the variation in the sample size included in each study.

The mean value of Left Atrial Volume Index (LAVi) (mL/m^2) in our study was calculated to be 33.17±6.74. It was comparable to the mean LAVi of 32.6±12.3 present in CKD patients in a study done by Hee *et al* [16]. Mean LAVi of 38.5±10.3 was present in a study by Kadappu *et al* [14], where stage 3 CKD patients were compared with risk factor matched subjects and normal healthy population. Mean LAVi of 34±15 was present in a study by Barberato *et al* [19], but these results were taken from a population on hemodialysis.

Kim *et al* [20] in a study evaluated the impact of an enlarged left atrium on all cause and CV mortality in 216 patients with CAPD. They found that increased left atrial volume index (>32mL/m^2) predicted all cause and CV mortality. This is in contrast to our study, where LAVi>34mL/m^2 was taken to depict increased cardiovascular involvement in CKD.

In our study, LAVi was correlated with increased diastolic dysfunction, as the disease progresses. In a study done by Barberato *et al* [19], it was demonstrated that LAVi was correlated with diastolic dysfunction severity in hemodialysis patients.

Our study used Body surface area (BSA) as an indexing method for left atrial volume. It was similar to the study done by Barberato *et al* [19] where they indexed left atrial volume with body surface area as well. Left atrial volume was also indexed to BSA in a study by Kadappu *et al* [14]. Similarly, BSA was used as an indexing method in a study by Hee *et al* [16]. In contrast, Tripepi *et al* [21] in a study estimated the CV risk in end stage renal disease (ESRD) using height as an indexing method for left atrial volume. It has been shown that adjustment to body size using height failed to nullify the gender influence on atrial size, unlike the adjustment to body surface area.

Many studies have proven the significance of LAVi assessment in end stage renal disease but LAV and LAVi as a marker of CV involvement in CKD stage 3, 4 and 5 is not well illustrated. Hence, in our study, we have assessed the values of left atrial volume index in stage 3, 4 and 5 CKD.

It was interpreted from our study that as the CKD stage increases, there is increase in the value of left atrial volume index (LAVi). This increment in LAVi values with progression of CKD from

stage 3 to stage 5 was associated with increase in diastolic dysfunction and decrease in ejection fraction.

Conclusion

It can be concluded that as the CKD stage increases, there is increase in the value of Left atrial volume index, which is associated with increased cardiovascular involvement. There is increase in diastolic dysfunction and decrease in ejection fraction as the CKD stage progresses from stage 3 to stage 5. Hence, earlier detection of increased left atrial volume index in CKD patients is important which will further help in deciding the prognosis of the patients.

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