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Original Research Article

Left ventricular dysfunction among chronic kidney disease patients: a cross sectional study

Tarun Rao, Mohit Karwa, Anil Wanjari*

Department of Medicine, Jawaharlal Nehru Medical College, Wardha, Maharashtra, India

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***Correspondence:**
Dr. Anil Wanjari,
E-mail: dranilwanjari@yahoo.com

ABSTRACT

Background: There is a significant worldwide burden of CKD; which is likely to increase further. Cardiovascular diseases constitute major cause of morbidity and mortality in CKD. LV dysfunction may be present despite the asymptomatic phase during the early stages of CKD. Thus, early detection of LV dysfunction and targeted interventions can improve prognosis in CKD.
Methods: This cross-sectional study was conducted among 250 CKD admitted patients. Echocardiographic examination was done to determine the systolic and diastolic function of LV. For LV systolic function ejection fraction and % fractional shortening were calculated and for LV diastolic function E/A, E/E', E deceleration time and IVRT were measured.
Results: Among 250 study subjects, 112 (47.8%) had systolic dysfunction and 138 (55.2%) had diastolic dysfunction. The prevalence of systolic as well as diastolic dysfunction increased significantly ($P<0.05$) with deteriorating renal function (39.1% for CKD stage 1 and 67.8% for stage 5 for systolic dysfunction, 34.8% for CKD stage 1 and 77.8% for stage 5 for diastolic dysfunction).
Conclusions: LV systolic and diastolic dysfunctions are significantly prevalent among CKD patients which increase with increasing severity of CKD. Hence, it is important to routinely screen these patients for LV dysfunction. The use of echocardiography can detect LV dysfunction at an early stage among the high-risk population of CKD to help plan appropriate strategies to slow the progression of cardiac dysfunction and improve prognosis.

Keywords: Chronic kidney disease, Echocardiography, Left ventricular dysfunction

INTRODUCTION

All over the globe chronic kidney disease (CKD) is imposing significant burden over healthcare. Trends pretend that it is likely to rise further in near future. The global estimate of CKD suggests a prevalence of 11-13%.[1] CKD is closely associated with cardiovascular disease (CVD).

CVD is the major cause of mortality and morbidity in CKD patients, plus CKD also accelerates the pathophysiological abnormality of CVD.[2,3] Usually, in the initial stages of CKD, individuals are asymptomatic. Even in the early stages of CKD, left ventricular (LV) dysfunction especially diastolic dysfunction is present.[4] The LV diastolic dysfunction is associated with increased heart failure and death risk in CKD.[5]

Although, LV systolic dysfunction in CKD is less common than LV diastolic dysfunction; still nearly 15% of CKD patients starting hemodialysis have been found to have LV systolic dysfunction. Like diastolic dysfunction,

LV systolic dysfunction is a risk for heart failure in CKD. LV systolic dysfunction is associated with severe CAD and is a future predictor of congestive heart failure and poor prognosis.[6] Proposed pathophysiology of LV dysfunction in CKD suggest that increased preload due to fluid overload, LV hypertrophy, myocardial fibrosis, microvascular abnormality, interstitial fibrosis, neuro-humoral (RAAS system) alterations are incriminatory.[7-9] Interventions aimed at these pathophysiologic mechanisms can reverse or at least slow down the deterioration in LV function.[10,11]

Hence, early detection of LV dysfunction with echocardiography in CKD patients can have a positive impact over the progressive decline in heart function provided appropriate therapy is instituted timely.

Thus, this study was aimed at determining the prevalence of LV diastolic and systolic dysfunction among CKD patients and evaluation of various parameters (E/A, E/E', E deceleration time, IVRT, LVEF and %FS) of LV diastolic and systolic dysfunction in various stages of CKD.

METHODS

This cross-sectional study was started after obtaining approval from the institutional ethics committee (IEC no 1589). The study was conducted among patients of CKD getting admitted in various wards of Medicine department of Acharya Vinobha Bhave Rural Hospital (AVBRH) attached to Jawaharlal Nehru Medical College (JNMC), Sawangi, Wardha, Maharashtra (India) from 1st September 2015 to 31st August 2017.

The calculated sample size was 215 and 250 patients were finally considered. After explaining study procedures and objectives to all the CKD patients informed written consent was taken. Inclusion criteria was patients of CKD admitted to medicine wards during the study period.

Exclusion criterion included those with known valvular heart disease or congenital heart disease (CHD), known coronary artery disease (CAD) or previous myocardial infarction, chronic obstructive or restrictive pulmonary disease, chronic liver disease, poor echo window, connective tissue disorder, HIV, hypothyroidism, hyperthyroidism, those with in-situ pacemaker or implantable cardioverter defibrillator, cancer, immunosuppressive therapy, hypertrophic cardiomyopathy, not willing to participate in study, already enrolled once in this study. Using study questionnaire; demographic details, relevant medical history and physical examination findings were recorded.

Investigations like kidney function tests, liver function tests, serum electrolytes, fasting blood glucose, postprandial blood glucose, complete blood count and peripheral smear, ultrasound abdomen, chest X-ray (CXR), electrocardiography (ECG), and echocardiography were done. Glomerular Filtration Rate (GFR) was calculated using the CKD-EPI online formula for GFR calculation and accordingly staging of CKD was done.[12-14]

For analysis purpose, we considered stage 3a and stage 3b as a combined stage and called it stage 3. On Echocardiography, for systolic function ejection fraction (EF) > 50% was considered normal and % fractional shortening (%FS) 30-50% was taken as normal.

For diastolic dysfunction, Doppler echo and tissue doppler were done. We calculated E/A (early diastolic mitral inflow velocity/late mitral inflow velocity), E/E' (early diastolic mitral inflow velocity/ septal mitral annular tissue early velocity), E wave deceleration time and intraventricular relaxation time (IVRT). Standard age-specific reference values and grading of diastolic dysfunction were used to determine normal and abnormal for these parameters as well as classification of LV diastolic dysfunction.[15,16]

The data was entered in Microsoft excel sheet. We used Stata version 13 software for statistical analysis and calculation of the prevalence of LV systolic and diastolic dysfunction. Means ± standard deviations (SD) of various parameters under study were calculated. $\chi 2$ test was used to compare categorical variable. A value of $p < 0.05$ was considered to indicate statistical significance.

RESULTS

Out of total 325 CKD patients admitted during study period, 75 were excluded (35 had diagnosed CAD, 21 were readmitted and already enrolled in the study, 15 had diagnosed CAD and 4 had COAD). 250 patients were finally considered for analysis.

All the study subjects were classified into three age groups (group 1- age 21-40 years, group 2 - 41-60 years, group 3- age more than 60 years).

Group 1 consisted of 27.2%, group 2 consisted of 52.8% and group 3 consisted of 20% of all participants. Of all the subjects; 114 (45.6%) were females and 136 (54.4%) were males. Mean age of study subjects was 49.7 years (SD 13.2). Hypertension was present in 77.6% (194) of subjects and 31.6% (79) of subjects were diabetic.

Table 1 depicts the EF, % FS, E/A, E/E', IVRT and E deceleration time across various age groups. Mean EF was found decreased with age and was higher among males compared to females across age groups. Mean %FS decreased with age as its mean in the age group 21-40 years was 36.4 (SD, 8.1) and for age group >60 years was 36.1 (SD, 8.7) and was higher among males in all age groups.

Table 1: Age wise distribution of EF, % FS, E/A, E/E', IVRT and E deceleration time.

	Age (in years) [Mean (S.D.)]								
	21-40 Years			41-60 years			>60 years		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
IVRT (msec)	76.5 (14)	76.7 (14.9)	76.6 (14.5)	76 (13.8)	76.3 (15.2)	76.2 (14.5)	70.8 (10.5)	70.4 (9.2)	70.6 (9.7)
E/E'	9.4 (2.4)	10.1 (2.5)	9.8 (2.4)	11 (2.8)	11.8 (2.9)	11.5 (2.9)	10.8 (2.7)	11.8 (2.8)	11.3 (2.8)
E dec (msec)	145.4 (23.5)	153 (35.8)	149.8 (31.2)	174.3 (41.3)	176 (43.1)	175.3 (42.1)	160.2 (42.4)	166.1 (41.9)	163.5 (41.8)
E/A	1.25 (0.34)	1.27 (0.25)	1.26 (0.34)	1.41 (0.53)	1.44 (0.57)	1.42 (0.55)	1.46 (0.53)	1.61 (0.52)	1.54 0.53)
EF	48.9 (3.9)	49.7 (2.6)	49.4 (3.2)	47.1 (7.7)	48.1 (6.8)	47.5 (7.2)	44.5 (8.9)	45.5 (9.5)	44.9 (9.2)
%FS	35.9 (8.2)	36.7 (8.1)	36.4 (8.1)	35.4 (7.6)	35.5 (6.8)	35.4 (7.2)	36.0 (9.1)	36.2 (8.5)	36.1 (8.7)

Table 2: CKD stage and LV dysfunction

Stages of CKD	Systolic dysfunction [Number (%)]				Diastolic dysfunction [Number (%)]			
	Absent	Present	OR	P value	Absent	Present	OR	P value
Stage 1	14 (61.9)	9 (39.1)	1	0.001	15 (65.2)	8 (34.8)	1	0.0001
Stage 2	21 (56.8)	16 (43.2)	1.18		16 (43.3)	21 (56.7)	2.5	
Stage 3	24 (55.8)	19 (44.2)	1.23		17 (39.5)	26 (60.5)	2.9	
Stage 4	27 (40.9)	39 (59.1)	2.25		16 (24.3)	50 (75.7)	5.9	
Stage 5	26 (32.1)	55 (67.8)	3.29		18 (22.2)	63 (77.8)	6.6	
Total	112 (47.8)	138 (55.2)			82 (32.8)	168 (67.2)		

Table 3: Echo measures of LV systolic and diastolic dysfunction in different stages of CKD.

	Chronic kidney disease				
	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
IVRT (msec)	74.3 (15.1)	75.2 (13.9)	72.6 (11.3)	77.6 (14.5)	74.6 (13.9)
E/E'	9.1 (1.9)	12.1 (3.7)	11.1 (2.5)	11.3 (2.1)	11.8 (3.1)
E dec (msec)	150.4 (32.2)	181.1 (47.3)	166.2(39.7)	168.4 (40.5)	161.4 (38.6)
E/A	1.25 (0.18)	1.33 (0.32)	1.18 (0.54)	1.34 (0.58)	1.65 (0.47)
EF	55.8 (3.5)	55.3 (5.2)	52.6 (4.2)	54.5 (5.5)	53.1 (6.1)
%FS	37.5 (12.3)	36.8 (9.1)	36.3 (7.2)	35.3 (6.3)	35.0 (6.7)

Table 4: Test characteristics of echo measures for LV diastolic dysfunction.

	E/A (%)	E/E'	E deceleration time	IVRT
Sensitivity	91.12 (85.87-94.55)	89.14 (83.67-92.94)	90.53 (85.17-94.09)	63.53 (56.07-70.39)
Specificity	81.48 (71.67-88.44)	80 (69.59-87.49)	72.84 (62.28-81.33)	96.25 (89.55-98.72)
Positive predictive value	91.1 (85.9-94.6)	91.23 (86.03-94.61)	87.43% (81.7-91.53)	97.3 (92.35-99.08)
Negative predictive value	81.6 (71.7-88.4)	75.95% (65.46-84.03)	78.67% (68.12-86.42)	55.4 (47.1-63.4)
Likelihood ratio of positive test	4.92 (3.78-5.17)	4.45 (3.91-5.1)	3.33 (3.05-3.65)	16.94 (8.72-32.9)
Likelihood ratio of negative test	0.11 (0.10-0.14)	0.14 (0.12-0.15)	0.13 (0.11-0.15)	0.39 (0.37-0.61)
Diagnostic accuracy	88% (83.4-91.5)	86.4 (86.1-90.1)	84.8 (79.83-88.72)	74 (68.23-79.05)

The E/A mean increased with age as the mean E/A in the age group 21-40 was 1.27 (SD, 0.25) and for age group >60 years was 1.54 (SD, 0.53). It was also found that the mean E/A was higher among females in all age groups. E deceleration time mean increased with age and was higher among males in all age groups. Mean IVRT was higher among males except those older than 60years. E/E' mean increased with age and was higher among males in all age groups.

As shown in Table 2, the prevalence of systolic dysfunction was 55.2% and diastolic dysfunction was 67.2%. We determined the trend of prevalence of LV dysfunction with stages of CKD and it was found that both systolic dysfunction (OR for stage 2 was 1.18 and for stage 5 was 3.29) and diastolic dysfunction (OR for stage 2 was 2.24 and for stage 5 was 6.6) increased in prevalence with more severe renal dysfunction. This trend was found to be statistically significant. Table 3 shows the mean along with standard deviation for EF, % FS, E/A, E/E', IVRT and E deceleration time in different stages of CKD. Among these parameters, mean EF decreased from 55.8 (SD, 3.5) in CKD stage 1 to 53.1 (SD, 6.1) in CKD stage 5, mean %FS decreased from 37.5 (SD, 12.3) in CKD stage 1 to 35.0 (SD, 6.7) in CKD stage 5, mean E/A increased from 1.15 (SD, 0.18) in CKD stage 1 to 1.67 (SD, 0.47), mean of E deceleration time increased from 150.4 (SD, 32.2) in CKD stage 1 to 181.1 (SD, 47.3) in stage 2 and then decreased to 161.4 (SD, 38.6) in CKD stage 5. Mean E/E' increased from 9.1 (SD, 1.9) in CKD stage 1 to 11.8 (3.1) in CKD stage 5. There was no specific trend observed with mean IVRT with increasing severity of CKD. Table 4 depicts the test characteristics of E/A, E/E', E deceleration time and IVRT for diagnosis of LV diastolic dysfunction (along with the confidence intervals). It was found that E/A had the highest sensitivity and diagnostic accuracy and had the lowest negative likelihood ratio while IVRT had the highest specificity, positive predictive value and positive likelihood ratio.

DISCUSSION

We aimed at determining the prevalence of LV dysfunction in CKD patients admitted in Medicine department of JNMC, Sawangi (Wardha) and its attached AVBRH hospital and we found that among 250 CKD patients admitted in this hospital during the study period, 112 (47.8%) had systolic dysfunction and 138 (55.2%) had diastolic dysfunction. We also found that the prevalence of systolic as well as diastolic dysfunction increased significantly ($P<0.05$) with deteriorating renal function.

Heart and kidneys are two organs which are very closely related in context of hemodynamic and regulatory functions. The renin-angiotensin aldosterone system (RAAS), antidiuretic hormone, endothelin, and the natriuretic peptides are among the many, which are responsible for interrelatedness of heart and kidney function.[17] As per international data, cardiac diseases account for 40% of deaths in dialysis population.[18] In this study, CKD patients were found to have a high prevalence of systolic (47.8%) and diastolic dysfunction (55.2%). The prevalence of systolic dysfunction increased with increasing severity of renal impairment (39.1% in CKD stage and 67.8% in CKD stage 5). A study by Nitin et al found that somewhat lesser i.e. 30.4% of CKD patients had systolic dysfunction and 56.5% had diastolic dysfunction. In that study and other studies also the prevalence of systolic dysfunction increased significantly with deteriorating renal function.[17,19] Singal et al have reported in their study that 23% Of study subjects had systolic dysfunction.[20] Similarly, in a study conducted by Avijit Debnath et al, 15% of the patients with mild/moderate CKD had systolic dysfunction while 48% of patients with severe CKD had systolic dysfunction.[21] However, some studies could not demonstrate significant systolic dysfunction in CKD patients.[22] These varying results could be explained on the basis of differences inherent in the studied population by these authors and the methodology to diagnose LV dysfunction and CKD stages.

In this study, we found that 67.2% of subjects had diastolic dysfunction. There was a trend of increasing prevalence of diastolic dysfunction with deteriorating renal function (34.8% in CKD stage 1 and 77.8% in CKD stage 5). A similar study conducted by Nitin et al had found that 51.85% of patients with mild/moderate CKD had diastolic dysfunction, whereas 82.6% of patients with severe CKD had diastolic dysfunction.[17] Losi et al in a cross-sectional study among patient on maintenance hemodialysis observed that nearly 40% of the patients had diastolic dysfunction.[23] Agrawal et had reported a prevalence of diastolic dysfunction of 30% IN early stages of CKD and 53.2% in late stages of CKD.[24] The differences between these observations can be explained on the basis of the different baseline characteristics of the population studied. These findings suggest that there is a significant burden of LV systolic and diastolic dysfunction in CKD patients.

Systolic function was assessed using LV ejection fraction and fractional shortening. Mean LVEF was within normal range in different stages of CKD but there was a declining trend with progressive stages of CKD. Similar trends had been noted by Agarwal et al also.[24] However, another study did not find this trend of declining LVEF with progressive CKD.[22] The present study found that mean % FS was almost similar in different stages of CKD, this observation is in contradiction to a few other studies which found a decline in % FS with progressive declining renal function.[25,26] This suggests that although the LV systolic function shows a decline with deteriorating renal function but this may not be evident by observing the change in the mean of LVEF or %FS.

In this study, we found that E/E' increased progressively with declining renal function (mean in CKD stage 1 was

9.1 and in stage 5 was 11.8). IVRT did not show a consistent trend with declining renal function. It's mean for various stages of CKD was 74.3 for stage 1, 75.2 for stage 2, 72.6 for stage 3, 77.6 for stage 4 and 74.6 for stage 5. Mean E deceleration time increased in CKD stage 2 compared to stage 1 (181.1 vs 150.4). There after demonstrated an approximate trend of decreasing E deceleration time with increasing severity of renal function decline (mean E dec time in stage3 was 166.3, in stage 4 was 168.4, in stage 5 was 161.4). This was probably because of increasing occurrence of diastolic dysfunction in CKD stage 2 compared to CKD stage 1 hence prolonging E deceleration time and the decline thereafter was due to increasing severity of diastolic dysfunction (associated with increasing LA pressure which resulted in abbreviated E deceleration time) with a progressive decline in renal function. Franczyk-Skóra et al had found in their study that E/E' ratio increased with declining renal function (CKD stage1/2 (6.7 ±1.5), CKD stage 3 (8.9 ±2.4), CKD stage 4 (11.5 ±4.0), CKD stage 5 (13.5 ±5.0), $p < 0.0001$). They also found a reduction in deceleration time (247.2 ±34.5 in CKD 1/2 vs. 197.4 ±61.0 in CKD IV, $p = 0.0005$) with decreasing renal function.[19] Laddha et al found that 61.4% of patients with the end-stage renal disease had diastolic dysfunction as denoted by E/A ratio of less than 0.75 or more than 1.8.27 A study done by Shah et al, have reported increasing diastolic dysfunction prevalence as determined by E/A ratio, with deteriorating renal function (58.5% in mild/moderate CKD and 82.6% in severe CKD).[17] Kim et al had documented a mean of 1.00(SD 0.66) for E/A, 14.6 (SD 6.9) for E/E' and 196.5(SD 62.4) for E wave deceleration time. They also found that abnormal E/E' can predict mortality and cardiovascular events in CKD patients.[5]

In present study, we found that E/A was the most sensitivity (91%) and IVRT was the most specificity (96%) parameter for the diagnosis of diastolic dysfunction. IVRT also had the highest positive predictive value (97%) and positive likelihood ratio (16.9). Diagnostic accuracy was highest for E/A (88%) which also had the lowest negative likelihood ratio. RICH-Q study has found that E/A ratio in children with the end-stage renal disease was less sensitive than E/E' to detect diastolic dysfunction. A recent study has reported that E/E' had a sensitivity of 73.5% and specificity of 57.8% and PPV and NPV were 75.75% and 55% respectively.[28] While Issaz et al had reported a sensitivity of 81%.29 Lee et al had reported that E/E' is more sensitive than E/A in detecting LV diastolic dysfunction.[30] So far, only few studies have documented the diagnostic values of various echo derived parameters of diastolic dysfunction. Studies have generally not documented the test characteristics for other parameters of echocardiography for diastolic dysfunction.

We have done this study among CKD patients and used certain echo measures to determine diastolic dysfunction. We have not studied others measures like pulmonary vein velocity. We used echo measures to establish diastolic dysfunction, hence when we determined test characteristics of different parameters we used echo derived diastolic dysfunction as standard. The test results would have been more reliable if other measures like invasively determined diastolic function would have been available. This was a limitation of present study and can be improved upon in future studies. Nevertheless, we have presented a significant report of LV function among CKD patients which can be used for present medical practice and used for future studies as well.

CONCLUSION

In conclusion, both LV systolic and diastolic dysfunction are significantly prevalent among CKD patients and these dysfunctions increase with increasing severity of CKD. Hence, it is important to routinely screen these patients for LV dysfunction. There are various modalities to determine LV dysfunction and echocardiography is one such important non-invasive method. Thus, the use of echocardiography can detect LV dysfunction at an early stage among the high-risk population of CKD to help plan appropriate strategies to slow the progression of cardiac dysfunction and improve prognosis. Test characteristics of various echo parameters of diastolic dysfunction suggest that they are a reliable mode of non-invasive diagnosis. Future studies focussed on comparing individual echo parameter compared with invasively determined diastolic dysfunction can further establish their reliability.

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