

Pattern and severity of left ventricular diastolic dysfunction in early and end stage renal disease patients with or without dialysis in rural population in South India

Prashant S. Sidmal*, Mallikarjun HP and KC Shekarappa

Department of General Medicine, Subbaiah Institute of Medical Sciences, NH 13, Purlae, Holehonnur Road, Shimoga-577222, Karnataka, India

***Correspondence Info:**

Dr. Prashant S. Sidmal,
Associate Professor
Department of General Medicine,
Subbaiah Institute of Medical Sciences,
NH 13, Purlae, Holehonnur Road,
Shimoga-577222, Karnataka, India.
E-mail: prashantsidmal@gmail.com

Abstract

Background: The chronic kidney disease (CKD) is a major risk factor for coronary artery disease (CAD) and left ventricle systolic dysfunction. Left ventricular (LV) diastolic dysfunction in CKD patients frequently leads to the development of congestive heart failure. The interaction between diastolic dysfunction (DD) and renal function in subjects with preserved systolic function is not well defined.

Objective: Our aim was to investigate whether renal insufficiency (RI) is associated with DD among patients with left ventricular ejection fraction (LVEF) > 50%, and to investigate whether there is a correlation between CKD and DD severity.

Methods: Eighty four CKD patients, aged 35-79 were examined by standard echocardiography. Subjects were divided into 4 groups depending on their estimated glomerular filtration rate (eGFR: ml/min/BSA) as follows: group 1 (60—89 ml/min/BSA), group 2 (30—59 ml/min/BSA), group 3 (15—29 ml/min/BSA) and group 4 (less than 15 ml/min/BSA), between 1/2/2014 and 30/4/2015. Glomerular filtration rate (GFR) was estimated using the MDRD formula. Patients with impaired relaxation (grade I) were compared to those with pseudonormal (grade II) or restrictive (grade III-IV) DD.

Results: Among 84 patients, 23 had GFR 60-89 ml/min/BSA; 16 had GFR 30-59 ml/min/BSA; and 19 had GFR 15-30 ml/min/BSA and 26 had GFR <15 ml/min/BSA. There was a significant correlation between worsening GFR and degree of diastolic dysfunction (DD) assessed by echo. Overall, 40.4% of the participants were female, 22 (26.1 %) had grade I, & 10 (11.9 %) had grade II, 16 (19%) had grade III and 36 (42.8%) had grade IV diastolic dysfunction. Almost all patients had some degree of diastolic dysfunction. With worsening of renal function, there was worsening of diastolic dysfunction seen. In patients with end stage renal disease many had grade IV diastolic dysfunction as compared to patients with early CKD. Grade I and II DD was commonly seen in group 1 and 2. But grade III and IV DD was commonly seen in group 3 and 4.

Conclusion: Worsening renal function was associated with greater degree of diastolic dysfunction and adverse clinical outcomes. Our Study indicated a clear and independent association between RI and DD. The severity of RI also tends to correlate with the severity of DD. And that LV diastolic dysfunction was observed even in patients with early stages of chronic kidney dysfunction.

Keywords: Chronic kidney disease, Echocardiography, Diastolic function, cardiovascular disease.

1. Introduction

CKD is associated with increased cardiovascular risk and mortality [1] and increased incidence of heart failure (HF). [2] Even a small reduction in kidney function is associated with higher risk of cardiovascular events and the strongest association is typically with HF. [3] Recent studies have shown an association between kidney function and HF risk across a wide spectrum of disease stages

from preclinical kidney disease to advanced CKD. [4,5] To evaluate kidney function, these studies used cystatin C. [6]

The pathogenesis of HF in persons with CKD has not been well characterized but likely relates to a combination of cardiac abnormalities and volume handling. [7] Among patients without HF, kidney function has been linked with structural

cardiac changes, including left ventricular hypertrophy (LVH). [8,9] Previous studies have evaluated the association of kidney function with LVH in patients with advanced disease approaching and requiring dialysis[10,11] as well as patients with earlier stages of disease[8]; LVH has been reported in over one-third of persons with CKD. [9] Diastolic dysfunction has also been studied in small cohorts of CKD patients. [12, 13]

Renal dysfunction is closely related to prognosis of cardiovascular disease (CVD) and conversely CVD patients often develop acute renal failure: this association is referred to as the cardiorenal connection. Chronic renal dysfunction has a negative effect on cardiac function and chronic kidney disease (CKD) is an important predictor of adverse outcome and increased morbidity in patients with chronic heart failure (CHF). [14-17] A stage classification for CKD has been proposed for assessing the degree of severity of renal dysfunction, and recent evidence indicates that a moderate decrease in glomerular filtration rate (GFR) to <60 ml/min/1.73 m² of body surface area is associated with an adverse outcome in CHF patients. [14-16]

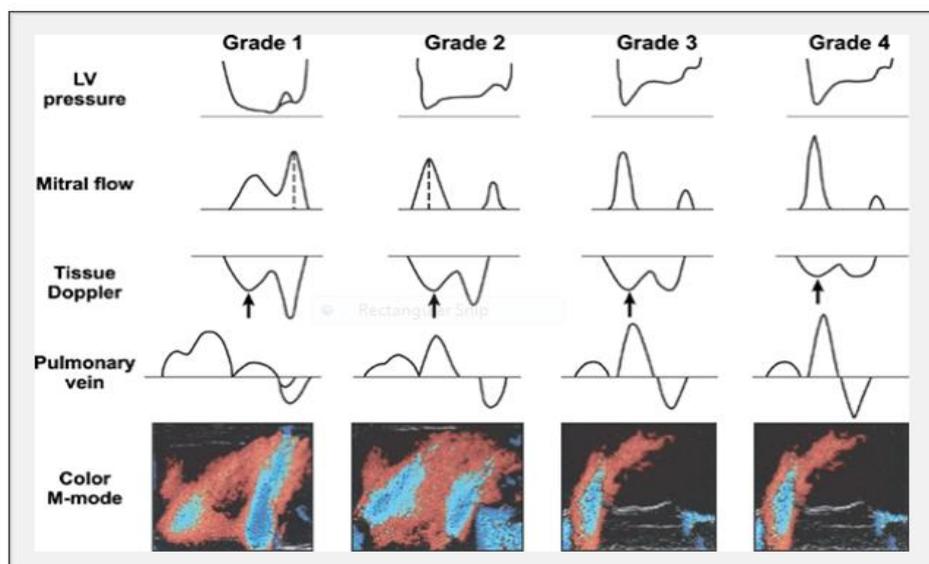
Diastolic dysfunction is frequently observed in CHF patients with or without CKD [18] and (tissue Doppler imaging) TDI has improved assessment of this condition. [19] Left ventricular diastolic dysfunction affects morbidity and mortality in CHF patients with CKD, and echocardiography may provide additional diagnostic data on ventricular function. [20] Myocardial dysfunction is common in patients with chronic kidney disease (CKD) especially in the end stage of renal failure and in dialysis patients. In CKD patients, left ventricular (LV) hypertrophy due to arterial hypertension and

chronic anemia is one of the main reasons for developing congestive heart failure. [21-24] It is especially important to consider heart failure with preserved LV systolic function, which dominates in this population of patients. Echocardiography as a routine noninvasive imaging method is useful in determining diastolic dysfunction.

Cardiovascular disease is the major cause of death in patients with advanced chronic kidney disease (CKD stages 4–5, eGFR <30 mL/min/1.73 m²), accounting for about 40% of deaths in international registries. [25] The risk of cardiovascular mortality is more than 10 times higher in this population compared with an age, sex, and race matched population. [26] Data on cardiovascular risk factors from the general population cannot simply be extrapolated to CKD patients as they are subject not only to traditional risk factors, but also to CKD-related risk factors such as inflammation, increased calcium and phosphorus products, uremic toxins, anemia, and fluid overload. [27-28] Additionally, CKD patients show a very high prevalence of vascular and valvular calcification which have been shown to be associated with increased arterial stiffness and adverse outcomes. [29-30]

Echocardiography provides a non-invasive assessment of cardiac structures and function. There is limited data on echocardiographic parameters predicting cardiovascular complications in patients with advanced CKD, including those who have not commenced dialysis. [31-33] Diastolic dysfunction can be graded as follows according to the diastolic filling pattern (as shown in figure 1)

Figure I. Grading of diastolic dysfunction



Grade 1 = impaired relaxation pattern with normal filling pressure; **Grade 2** = pseudonormalized pattern; **Grade 3** = reversible restrictive pattern; **Grade 4** = irreversible restrictive pattern

Abnormal left ventricular (LV) filling patterns (grades 1 to 4). Grading of diastolic dysfunction and filling pattern based on mitral inflow, mitral annulus velocity, pulmonary vein velocity, and color M-mode of mitral inflow. Arrow, Reduced early diastolic velocity (E') of mitral annulus in all stages of diastolic dysfunction (*Courtesy Echo Manual, The, 3rd Edition, Oh, Jae K.; Seward, James B.; Tajik, A. Jamil*)

2. Methods

2.1 Study population

A total of fifty four CKD patients aged 35 to 79 years were enrolled in this study during the period from 1st February 2014 to 30th April 2015, coming from rural background attending the tertiary care centre in South India. This study project was approved by the ethics committee. A written informed consent was obtained from each patient. Subjects were counseled and explained about the objectives of the study by a qualified medical doctor. Detailed personal history was taken using a standard questionnaire. Exclusion criteria are --patients with atrial fibrillation, systolic left ventricular dysfunction, CHF, myocardial infarction, cardiomyopathy, or valvular disorders. Systolic left ventricular dysfunction is defined as ejection fraction less than 50%.

2.2 Demographic and clinical data

Baseline data from patients were collected like-- age, gender, blood pressure (BP), hemoglobin (Hb), serum creatinine (Cr), and blood urea nitrogen (BUN). Patients were considered to be hypertensive based on European Society of Hypertension guidelines ($\geq 140/90$ mmHg) or if they were taking antihypertensive medication. [34]

2.3 CKD and estimated GFR

The subjects were divided into 4 groups based on estimated eGFR:

Group 1 (60—89 ml/min/BSA),

Group 2 (30—59 ml/min/BSA),

Group 3 (15—29 ml/min/BSA),

Group 4 (<15 ml/min/BSA)

Patients in group 1 were defined as having early stage CKD based on the US National Kidney Foundation Kidney Disease Outcome Quality Initiative[35] and those in groups 2 to 4 were considered to have CKD. The eGFR was calculated using the abbreviated Modification of Diet in Renal Disease Study Equation: $eGFR$ (ml/min/1.73 m² of body surface area) = $186 \times (\text{serum creatinine in mg/dl})^{-1.154} \times (\text{age in years})^{-0.203} \times (0.742 \text{ for female})$ subjects.[36] CKD or renal insufficiency (RI) was diagnosed in subjects with an $eGFR < 60$ ml/min/1.73 m².

2.4 Electrocardiography

A 12-lead surface ECG was obtained from all subjects in the supine position. ECG was recorded at a paper speed of 50 mm/s.

2.5 Echocardiography

Diastolic function of the heart was assessed and recorded. Echocardiographic studies were performed using a HDI 3000 (Philips ATL, Bothell, WA, USA) equipped with 2 to 4 MHz probes allowing M-mode, color Doppler, two dimensional, and pulsed Doppler measurements. Echocardiography was performed according to the guidelines of American Society of Echocardiography. [37] Mitral inflow velocity was traced and the following variables were derived: peak early (E) and late (A) transmitral flow velocities, the ratio of early to late peak velocities (E/A), and deceleration time of E velocity. [38-40] The echocardiographies of the patient on dialysis were performed before dialysis. Mitral inflow patterns: - The normal E/A ratio is between 1 and 2.

Grade 1 diastolic dysfunction (Impaired myocardial relaxation): The E/A ratio is < 1, with a prolonged deceleration time (Dct) (>240ms). In the tissue doppler assessment, e' is also reduced with a resultant E/e' ratio (medial) <8, suggesting a normal LA pressure. The D wave of the pulmonary venous inflow is smaller than the S wave and the atrial reversal (AR) wave is normal.

Grade 2 diastolic dysfunction (Pseudonormalized pattern): When diastolic LV function deteriorates, LV compliance progressively decreases and there is an increase of LA pressure and the diastolic filling pressure. The transmitral E wave velocity progressively increases and the Dct decreases. As it does so, it goes through a phase that resembles a normal filling pattern. The E/A ratio is between 1 and 2 and the Dct between 160 and 240ms. This pseudo-normal pattern is a transition pattern from impaired relaxation to restrictive filling and is a result of a moderately increased LA pressure superimposed on a relaxation abnormality. The following clues help distinguish this from a normal filling pattern-- E/e' ratio (medial) >15 and pulmonary venous flow AR >25cm/sec and longer than transmitral A wave.

Grade 3 and 4 diastolic dysfunction (restrictive pattern): With more severe diastolic dysfunction, LV compliance reduces and LA pressures rise. The low compliance of the LV causes a rapid increase in the early LV pressure and a shortened inflow and DT. The E/A ratio is > 2. Dct is < 160ms. The high LA pressure manifests as a E/e' ratio >15 at the medial annulus. Forward diastolic pulmonary vein flow stops in mid-late diastole and during atrial contraction there is a significant flow reversal resulting in a prolonged

AR. A reversal to grade 1 or 2 on reducing the preload by performing Valsalva manoeuvre or administering nitroglycerine suggests reversibility of the cardiac restriction and is termed grade 3. Diastolic filling should be graded as irreversible (grade 4) in the absence of such a reversal.

2.6 Statistical Analysis

SPSS for Windows, version 16, was used for data analysis. The qualitative data were analyzed by chi-square, Fisher's exact test and the Student's t test for continuous variables. Continuous variables were presented as mean \pm standard deviation (SD);

categorical variables were presented as percentages. P value <0.05 was considered significant.

3. Results

The subjects were classified into four groups based on eGFR. There was no significant difference in gender, diabetes mellitus, diastolic BP, or frequency of hypertensive patients among the four groups (Table 1). BUN and Cr increased in parallel with the severity of kidney dysfunction. Diastolic BP was elevated in all groups.

Table I. Patient characteristics

Item	Group 1 (n = 23)	Group 2 (n = 16)	Group 3 (n = 19)	Group 4 (n = 26)
Age	54 \pm 8.2	64 \pm 9.1	68 \pm 7.2	74 \pm 6.3
SBP	149 \pm 17	156 \pm 17	159 \pm 16	168 \pm 11
DBP	98 \pm 9	96 \pm 7	96 \pm 9	98 \pm 8
DM (%)	8	4	7	5
Hb (g/dl)	11.1 \pm 2.0	10.1 \pm 1.8	9.2 \pm 2.0	8.3 \pm 1.5
BUN (mg/dl)	16.2 \pm 3.2	19.9 \pm 3.8	36.4 \pm 6.1	49.3 \pm 14.8
S Cr	1.1 \pm 0.9	1.9 \pm 1.3	2.9 \pm 2.6	7.6 \pm 3.4

As shown in Table II, as the age advances the risk of progression to end stage renal disease increases. Systolic BP was seemed to increase with duration of disease and age of the patient.

Distribution of diabetes was similar in the groups. Hemoglobin was found to decrease as disease worsened.

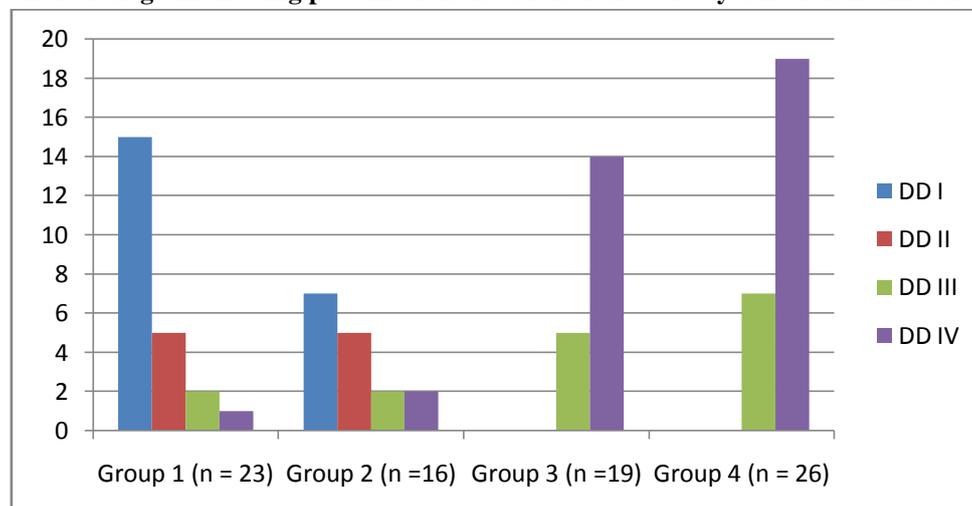
Table II. Distribution of diastolic dysfunction in various age groups and by gender

Group	Diastolic function							
	DD I		DD II		DD III		DD IV	
	Number	%	Number	%	Number	%	Number	%
<40	2	2.3	1	1.1	3	3.5	6	7.1
40-60	9	10.7	2	2.3	5	5.95	12	14.2
>60	11	13	7	8.3	8	9.52	18	21.4
Male	12	14.2	7	8.3	10	11.9	22	26.1
Female	10	11.9	3	3.5	6	7.1	14	16.6

Figure II shows the categories of diastolic dysfunction by level of eGFR. Almost all patients had one or the other type of diastolic dysfunction. As kidney function worsened, there was progressive worsening of diastolic dysfunction. More patients

with grade IV diastolic dysfunction were found in Group 3 and 4, than in group 1 or 2. As disease progressed, severity of diastolic dysfunction also worsened.

Figure II. Bar diagram showing pattern of distribution of diastolic dysfunction in different groups



There was an insignificant relation between gender and diastolic dysfunction and it was more frequent in male patients (Table II). There was a significant relation between diastolic dysfunction and age ($P=0.045$). The age group of >60 years was the most frequent group of diastolic dysfunction. Majority of CKD patients in this group had grade IV diastolic dysfunction (Table II). As shown in figure II, grade I and II diastolic dysfunction was commonly seen in group 1 and 2. But grade III and IV diastolic dysfunction was commonly seen in group 3 and 4.

4. Discussion

Diastolic dysfunction is a complex process that arises from numerous interrelated contributing factors such as pressure variations in the ventricle, cardiac preload, afterload, ventricular relaxation and compliance. [41] Diastolic dysfunction is an abnormality of relaxation, filling, or distensibility of the left ventricle that is associated with augmented cardiovascular mortality. [42-44] Transmitral pulsed Doppler is a non-invasive method of evaluation of diastolic dysfunction, but is influenced by factors such as the loading condition of the left atria and heart rate.

Our study results show that left ventricular diastolic dysfunction is present in all patients with CKD, including those with an early stage of the disease. These results indicate that Doppler indices can detect subtle changes of diastolic function caused by kidney dysfunction. We also found that diastolic dysfunction got worsened in parallel with the severity of kidney dysfunction.

These results suggest that the left ventricle filling pressure may be higher in groups 3 and 4 than in groups 1 or 2. However, there is a possibility that it is affected by intrinsic volume overload in hemodialysis patients. Even a moderate decline in kidney function is associated with a significantly worse prognosis in patients with underlying CHF [45-47] but only a few clinical studies have attempted to elucidate the underlying mechanisms. Diminished renal perfusion is frequently a consequence of hemodynamic changes associated with heart failure and its treatment. [48]

In addition to the adverse effects of heart failure on renal function, renal insufficiency adversely affects cardiac function, producing a vicious circle in which renal insufficiency impairs cardiac performance, which then leads to further impairment of renal function. As a result, kidney insufficiency is a major determinant of the progression of heart failure, congestion, recurrent decompensation, and hospitalization. The etiology of heart failure in patients is complex and several

factors may be at work in CKD patients. [46, 49-51] Cardiovascular disease is the leading cause of death in patients with advanced CKD. [52]

The pathophysiology of cardiac disease in CKD is related to the interaction of multiple factors including hypertension, chronic volume overload, anemia, presence of an AV fistula in patients on dialysis, as well as metabolic factors such as acidosis, hypoxia, hypocalcaemia and high levels of parathyroid hormone. [53,54]

Morphological changes in the heart include- LVH, advanced coronary atherosclerosis microvascular disease and diffuse interstitial myocardial fibrosis. [55,56] These abnormalities are common in CKD patients and have been shown to be predictive of mortality. [57,58] Assessment of diastolic function by echocardiography has shown a high incidence of abnormalities in dialysis and non-dialysis CKD patients. [59,60] Similar to our study, some investigators have found abnormalities in tissue Doppler velocity in virtually all patients with CKD, suggesting a degree of subclinical myocardial disease in all such patients. [61] In the CRIC study (stage 2-4 CKD), diastolic function was abnormal in 71% of patients. [62] Patients with abnormal diastolic function have been found to have increased integrated backscatter which is a measure of collagen content of myocardial tissue. [63]

5. Limitations

We used conventional routine echocardiographic examination methods to assess the left ventricular diastolic function in CKD patients. The number of patients was not the same in each group and the duration of renal dysfunction, hypertension, and diabetes were not similar in each group. These factors may have affected the statistical analysis. This was a single centre study and our patient population was relatively small. Further studies with larger samples are recommended. Long term follow-up after discharge is needed to assess the improvement of diastolic dysfunction with improvement in clinical status.

6. Conclusions

We conclude that left ventricular diastolic dysfunction occurs in patients with CKD and that doppler indices can be used to detect subtle changes of diastolic function due to kidney dysfunction. Patients with advanced CKD have a high incidence of structural cardiac abnormalities including diastolic dysfunction. These factors are associated with increased mortality and adverse cardiac events compared to CKD patients without these factors, even in the non-dialysis population. We therefore

suggest routine evaluation of diastolic function by echocardiography, and screening for vascular risk factors in all CKD patients. Whether early identification of these risk markers and intervention in CKD patients will lead to improved outcomes should be the subject of further investigation. We conclude that the patients with CKD developed a stepwise reduction in global diastolic function and, more importantly, that this happens before the onset of a clinical heart failure.

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Ethical approval: Approved

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