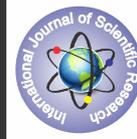


## Asymptomatic LV Dysfunction in patients of Chronic Kidney Disease on Maintenance Hemodialysis



### Cardiology

**KEYWORDS:**

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### ABSTRACT

*Aims: To identify subclinical left ventricular (LV) myocardial dysfunction using speckle tracking echocardiography (STE) in patients with chronic kidney disease (CKD), preserved LV ejection fraction (LVEF), and no cardiovascular history or symptoms.*

*Methods: 73 patients satisfying the inclusion criteria were recruited in this cross sectional Exploration study. Their Ecocardiography (ECHO) was done taking both conventional 2D ECHO parameters and LV strain imaging parameters using Speckle Tracking Imaging(STE) on GE Vivid T8 Echo Machine in KEM Hospital, Mumbai.*

*Results: Global longitudinal systolic strain was the most important parameter to be studied. Values of GLS were least among the CKD stage 5D group and were statistically significant. GLS in CKD 5D was  $-9.1 \pm 2.01$ . This differed significantly from control group ( $p$  value  $< 0.005$ ).*

*.Global longitudinal strain rate at the end of diastole was  $1.04 \pm 0.33$  in CKD 5D. This was significantly less as compared with the controls. ( $p$  value  $0.005$ ). LVMI was  $75 \pm 22.3$  for CKD 4/5 and  $120 \pm 25.2$  for CKD 5D due to chronic long standing hypertension which increased the LV mass.*

*This also correlates with percentage of patients with left ventricular hypertrophy. Along with significant diastolic dysfunction. Grade 3. Even The number of segments with diastolic dysfunction were more in the CKD groups compared with controls. ( $p$  value  $< 0.005$ ).*

*Patients who received more number of dialysis had lower values of GLS indicating such patients had significant asymptomatic LV dysfunction.*

*Conclusion: In this cohort of patients with advanced CKD, GLS is a more sensitive predictor of overall and CV mortality compared to EF. Studies of larger populations in CKD are required to confirm that GLS provides additive prognostic value in patients with preserved EF.*

**INTRODUCTION:** Approximately 3.8% of the Indian population are estimated to have chronic kidney disease (CKD)(1). Similar prevalence of CKD has been reported in studies from the UK,(2) Asia,(3) and Australia,(4) highlighting the worldwide epidemic nature of the disease. The landmark study of Go et al (5) on 1, 120, 295 US Adults showed an independent graded association between estimated glomerular filtration rate (eGFR), cardiovascular events, and death, highlighting the need for early detection and treatment of cardiovascular risk factors and disease in these patients. Early identification of ischaemic heart disease in CKD patients, however, is not an easy task as they are less likely to report classic angina/myocardial infarction (MI) symptoms.(6).

Longitudinal LV mechanics, which are predominantly governed by the subendocardial region, are the most vulnerable and sensitive to the presence of myocardial disease. The mid-myocardial and epicardial function may remain relatively unaffected initially, hence circumferential strain and twist may remain normal or show exaggerated compensation in an attempt to preserve LV systolic performance. Loss of early diastolic longitudinal relaxation attenuates LV diastolic performance, producing elevation in LV filling pressures and a phase of predominant diastolic dysfunction (DD).(7),(9)

Conventional 2D ECHO Left Ventricular Hypertrophy (LVH), Visualised Ejection Fraction (EF) and LV Diastolic dysfunction (DD) both of which along LV Systolic dysfunction predict adverse cardiovascular outcomes in patients with Chronic kidney disease.

Very few studies attempted to identify subclinical markers of myocardial disease using STE. Two small studies which compared STE markers in CKD patients and controls with normal LVEF

identified reduced global longitudinal and circumferential systolic strain.(17,18) In another study, Edwards et al.19 using tissue Doppler myocardial imaging, demonstrated reduced global strain and strain rate (SR) in patients with early CKD stages. Even though of interest, the aforementioned studies are small and under-powered, whereas some novel elements of deformation (e.g. twist) were not investigated.

In the present study, we aimed to conduct a comprehensive analysis of conventional and speckle tracking two-dimensional (2D) echocardiographic parameters in CKD patients (of all stages) who have a preserved LVEF and no known history or symptoms of cardiovascular disease.

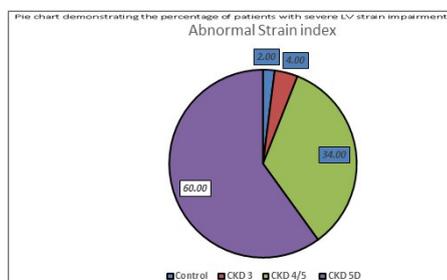
**Methods:** 73 Patients over period of 1 year from feb 2015 to February 2016 were included attending nephrology OPD were taken upon for echocardiography study. Patients with clinical or echocardiographic evidence of LV systolic dysfunction (Simpson biplane LVEF  $< 55\%$ ), presence of regional wall motion abnormalities, significant valvular abnormalities (moderate or severe), presence of atrial fibrillation (AF) or flutter, known pulmonary hypertension, congenital heart disease, any cardiomyopathy, pericardial disease, or inadequate echocardiographic acoustic windows were excluded from this study. We also recruited age ,sex matched controls that had no known history of kidney or cardiovascular disease, or Echocardiographic evidence of LV systolic dysfunction. Written informed consent was obtained from all participants.

**Data Collection :** Using detailed history, physical examination and lab measurement and detailed 2D echocardiography including strain echocardiography at baseline. Conventional Echocardiography :A comprehensive transthoracic 2D and Doppler echocardiography examination was performed using the Vivid T 8 (GE Vingmed

Ultrasound, Horten, Norway) as per the American Society of Echocardiography guidelines.(22) LV mass was calculated according to Devereux's formula.(23) Relative wall thickness (RWT) was calculated using the following formula:  $[2 \times \text{posterior wall thickness (LVPWT)}] / [\text{LV internal diameter in diastole (LVIDd)}]$ . Concentric LVH was defined using the 2D Conventional echocardiographic findings in CKD include method (22) as left ventricular mass index (LVMI) more than 116 g/m<sup>2</sup> in men and more than 96 g/m<sup>2</sup> in women, with RWT more than 0.42; Eccentric LVH was defined as LVMI more than 116 g/m<sup>2</sup> in men and more than 96 g/m<sup>2</sup> in women, with RWT less than 0.42.(24). Diagnosis (and types of global DD were based on the current guidelines.().

Strain echocardiography ; Speckle tracking analysis was performed by the customized software for Vivid (2D-strain EchoPac PC v.7.0.1, GE Healthcare, Horten, Norway). During image acquisition, 60–80 frames/s were selected, the focus was positioned at an intermediate depth to optimize the images, and the sector depth and width were adjusted to include as little as possible outside the region of interest.(26). The systolic duration was defined as from the onset of QRS of the ECG to the aortic valve closure (AVC), which was determined automatically by the software and validated by the operator. Longitudinal deformation values (strain and SR) were obtained from the three apical views and circumferential values from the basal, mid, and apical short-axis planes. Global strain values were calculated from the average of the 18 segments in the longitudinal or circumferential planes.

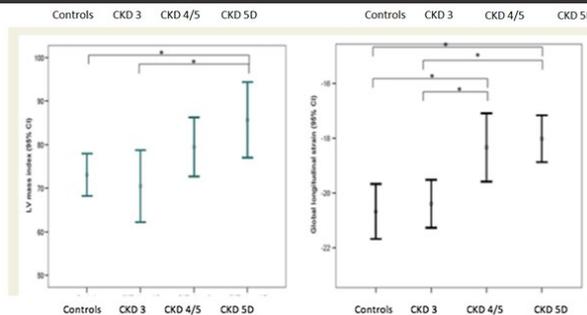
A global longitudinal strain (GLS) absolute value of, 16% was considered pathological (GLS 21.6%).(27). Intra- and inter-observer reproducibility and mean differences were analysed from repeated measurements performed by the same observer at two different time points and by a second blinded independent observer in 30 randomly selected participants, respectively.



**Follow up :** All CKD participants were followed up for a mean time of 30.7 + 11.7 months for major adverse cardiovascular events (MACEs), including all-cause mortality, acute coronary syndromes, stable angina requiring revascularization [either using percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG)].

**Baseline Characteristics of all patients**

Parameter	Controls (n=36)	CKD 3 (n=26)	CKD4/5 (n=24)	CKD5D (n=23)
Age	37.4±3.2	48.8±5.1	56.9±2.5	57.4±2.2
Male gender%	47.4	44.4	55.3	57.8
BMI	25.6±4.3	26.6±3.5	27.5±5.2	26.9±4.2
eGFR	110.6±10.9	45.3±9.3	35.2±7.2	7.0±5.5
Systolic BP	124±10.6	134±20.5	140±12.2	148.5±12.5
Hypertension%	26	41.5	88.6	80.9
Diabetes%	0	20.7	60.5	43.6
Aspirin%	0	20.9	44.1	40.1
Ace inhibitors%	0	37.9	-	-
Beta blockers%	0	20.8	25.2	29.2
Loop diuretics%	0	17.2	29.9	31.5
Number of Hemodialysis received	0	0	0	150-200



**Figure1: Increased LVmass index and reduced globally Longitudinal strain in chronic kidney disease patients (observed values+95% confidence intervals, \*P .005 after Bonferroni correction in the univariate model).**

**Results**

The demographic data which included age, sex etc varied among the different groups.

The average age for controls was 37.4, for CKD stage 3, it was 44.4; for CKD stage 4/5 it was 56.9 and for CKD stage 5D it was 57.4.

A male predominance was observed mainly across CKD stage 4/5 and stage 5, it was 55.3 and 57.8 percent respectively.

BMI was more or less same across all the groups. It varied from 25 to 29.

eGFR was more than 90 among all the controls. It decreased as per the CKD groups. With the decrease in eGFR there was significant increase in number of patients with asymptomatic LV dysfunction as demonstrated by decreasing values of GLS.

BP was on the higher

side, particularly among the patients with CKD stage 4/5 and CKD 5D.

Diabetic population was maximum in group with CKD 4/5.

Aspirin was used maximally in group with CKD 4/5 whereas loop diuretics were used maximally in group 5D. This group i.e 5D is the group which received hemodialysis. On an average these patients received 150-200 dialysis over the year.

Results from the echocardiographic parameters were statistically significant among the various groups.

Global longitudinal systolic strain was the most important parameter to be studied. Values of GLS were least among the CKD stage 5D group and were statistically significant. GLS in CKD 5D was -

GLS and its relationship with number of hemodialysis received

9.1±2.01. This differed significantly from control group (p value <0.005).

This decreasing value of GLS indicates that patients with CKD had asymptomatic LV dysfunction.

Global longitudinal strain rate at the end of diastole was 1.04±0.33 in CKD 5D. This was significantly less as compared with the controls. (p value <0.005).

LVMI was 75±22.3 for CKD 4/5 and 120±25.2. both these values indicate that LV mass was more in ckd groups possibly due to chronic

longstanding hypertension which increased the LV mass.

Grade 3 Diastolic dysfunction was present only in CKD 4/5 and CKD D. It was statistically significant as compared with controls. Even the number of segments with diastolic dysfunction were more in the CKD groups compared with controls. (p value < 0.005).

E/e' septal was more in CKD 5D and CKD stage 4/5 and the values were statistically significant.

Patients who had received more than 150 dialysis particularly had more LV dysfunction.

## Discussion

This is the first of its study from India showing comprehensive study of subclinical STE abnormalities in CKD patients with preserved LVEF and no previous history or symptoms of cardiovascular disease. STE demonstrated that, despite normal LV systolic function on conventional echocardiography, a reduced GLS and GLSRs were observed among CKD patients, parameters which were independently associated with eGFR. Almost a third of patients with CKD stages 3–5 had impaired GLS, whereas DD was more extensive with worsening eGFR. Patients with impaired GLS had increased rates of MACE during follow-up. The bulk of CKD patients has normal LV systolic function when assessed with conventional echocardiography (90%). A study from Ahmed et al identified increased mortality among CKD patients with reduced LVEF, but even more so, in those with preserved LV systolic function but presence of DD. Using conventional 2D echocardiography, CKD patients demonstrate increased prevalence of LVH, 11, 14, 30 particularly in late stages. 18 Prevalence of LVH in CKD patients correlates with the degree of renal impairment 31 and predicts future mortality and incident systolic heart failure. 32 Our data concur with findings from previous studies, suggesting an inverse association between eGFR and LVMI. Hayashi et al. 29 in a small study of 22 CKD stage 1–3 and 18 CKD stage 4–5 patients identified increased prevalence of DD (63 and 66%, respectively), defined as e' septal < 8 cm/s. Unlike the present, most studies, 12, 29, 33 when presenting data on DD, omit grading according to the established guidelines. (25) In our cohort, DD is more common in CKD stages 3–5 (70%) with Grade I (impaired relaxation) being the most prevalent (40%), followed closely by Grade II (pseudonormal; 30%). In a small number of late-stage (pre-dialysis) CKD patients 17 (n = ¼ 20) with preserved LVEF, there was reduced GLS and GCS when compared with healthy volunteers. In an attempt to identify subclinical LV dysfunction in early-stage CKD, Edwards et al. 19 compared the longitudinal deformation indices of 40 CKD stage 2/3 patients (with no history of CVD or DM) with 30 healthy controls. Once again, even though LVEF was similar in the two groups, there was reduced GLS and GLSRs among CKD patients. The above studies included small numbers of CKD patients and only focused on few elements of myocardial deformation. In the present study, we identified new patterns of LV deformation among asymptomatic CKD patients. During systole, the reduced GLS and GLSRs were compensated by increased LV twist and twist rate. These findings suggest a pattern of subendocardial injury the effects of which are compensated by the epicardial myocardial fibres (increased LV twist). During diastole, GLSRs were significantly associated with eGFR, suggesting an impaired early diastolic filling in CKD. The E/e' average ratio was significantly, independently, and inversely correlated with eGFR, suggesting increasing filling pressures in later CKD stages. Study limitations Strengths of the present study include the measurement of state-of-the-art deformation parameters both in systole and diastole that allow pattern inferences, and the detailed clinical characterization of the cohort. Limitations include the cross-sectional nature of the associations between STE parameters and CKD stage, which do not allow directionality of inferences and should be seen as 'hypothesis generating'. Secondly, even though our controls were significantly younger compared to CKD patients, we ensured that age and risk factor adjustments were carried out every time conventional or STE parameters were compared. Thirdly, even though our GLS data in the

normal group are directly comparable to those presented in the Japanese Ultrasound Speckle Tracking of the Left Ventricle (JUSTICE) Study they differ from the figures presented in the large HUNT study where a different vendor is used. This emphasizes once again the importance of ongoing efforts to standardize speckle tracking methodologies across different vendors. Finally, even though patients recruited in the current study were asymptomatic from the cardiovascular point of view, with no previous history of ischaemic heart disease and a structurally normal echocardiogram, the presence of significant coronary artery was not ruled out with a functional or invasive test.

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