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Original Paper

Impaired Left Ventricular Global Longitudinal Strain among Patients with Chronic Kidney Disease and End-Stage Renal Disease and Renal Transplant Recipients

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Keywords
Left ventricular systolic dysfunction · Speckle echocardiography · Left ventricular global longitudinal strain · Chronic kidney disease · Kidney transplantation

Abstract
Background: Although heart failure is the most prevalent cardiovascular disease associated with adverse outcome in chronic kidney disease (CKD) and after kidney transplantation, left ventricular (LV) systolic function is often preserved in renal patients. The aim of this study was to evaluate global longitudinal strain (GLS), which is reportedly a more accurate tool for detecting subclinical LV systolic dysfunction, in patients with various degrees of renal function impairment, including kidney transplant recipients (KTRs). ***Methods:*** This prospective study evaluated demographic, clinical, and ultrasound data, including the assessment of LV GLS and mitral E peak velocity and averaged ratio of mitral to myocardial early velocities (E/e'), of 70 consecutive renal patients (20 with stage 2–4 CKD, 25 with end-stage renal disease on hemodialysis [HD], and 25 KTRs). All patients had an LV ejection fraction ≥50% and no history of heart failure or coronary artery disease. We used multivariable logistic analysis to assess the risk of compromised GLS. One hundred and twenty control subjects with or without hypertension served as controls. ***Results:*** A compromised GLS <–18% was shown in 55% of patients with stage 2–4 CKD, 60% of HD patients, and 28% of KTRs, while it was 32% in hypertensive controls and 12% in non-hypertensive controls ($p < 0.0001$). Patients with HD had higher systolic pressure and a significantly greater prevalence of increased LV mass and diastolic dys-

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function. In renal patients, E/e' (p = 0.025), and LV mass index (p = 0.063) were independent predictors of compromised GLS at logistic regression analysis. E/e', systolic artery pressure, and LV mass also exhibited the greatest areas under the curve on receiver operating characteristic analysis to identify a compromised GLS. ***Conclusions:*** Renal disease proved to be associated with early and subclinical impairment of LV systolic function, which persists after starting dialysis and even in spite of successful kidney transplantation. An increased E/e' resulted to be the most powerful independent predictor of abnormal GLS.

Introduction

Cardiovascular (CV) disease still remains the most important cause of morbidity and mortality in patients with renal disease [1], and this scenario persists even after successful kidney transplantation [2]. Heart failure (HF) is the most prevalent CV disease observed in renal patients, either in early chronic kidney disease (CKD) or in end-stage renal disease (ESRD) and also in kidney transplant recipients (KTRs), and is associated with poor outcome [3–6]. Nevertheless, left ventricular (LV) systolic function as estimated according to conventional methods is preserved in a great proportion of patients with early CKD and in dialysis patients and even improves after grafting [7–10]. Thus, it has to be ascertained whether a more accurate assessment of systolic function may significantly improve the detection of early subclinical LV systolic dysfunction in patients with renal disease, who are reportedly at increased risk of future HF or other major CV events.

Global longitudinal strain (GLS), which is the negative ratio of the maximal change in LV longitudinal length in systole to the original length as assessed by speckle tracking echocardiography, proved to be superior to standard LV ejection fraction (EF) in predicting cardiac events and all-cause mortality in the general population [11, 12]. Abnormal GLS was independently associated with both all-cause and CV mortality also in patients with CKD and those undergoing hemodialysis (HD) [13, 14].

However, to our knowledge, this is the first study to evaluate LV function by speckle tracking echocardiography in subjects with different degrees of renal dysfunction, including those with functioning kidney transplant, with the aim of ascertaining the role of renal impairment in early LV systolic dysfunction of subjects with normal standard EF but traditionally at greater risk of subsequent CV disease.

Methods

Patients

Consecutive renal patients with no history of major clinical events in the last 6 months and who underwent routine echocardiography in the same previous 6 months were considered eligible for this study. Enrolment included HD patients, patients with non-dialysis CKD, and KTRs. Patients attending our tertiary care Nephrology Outpatient Unit were selected if they had stage 2–4 CKD according to estimated GFR calculated by the CKD-EPI formula [15], whereas KTRs were considered eligible if they had functioning graft (serum creatinine ≤2 mg/dL in at the last three consecutive assays) for 2 years at least.

For means of comparison, 50 subjects with normal renal function and arterial hypertension and 60 normotensive healthy controls were also studied. Hypertensives were evaluated since arterial hypertension proved to be associated with subclinical systolic dysfunction [16, 17].

Eligible patients had to have an LV EF ≥50%. Diabetes mellitus and hypertension were defined according to the current guidelines.

Patients were excluded if they had a history of acute coronary syndromes, angina, or revascularization procedures or evidence of segmental wall motion abnormalities at echocardiography, or a history of HF. Other exclusion criteria were: significant aortic or mitral valve disease, severe mitral annular calcification, hypertrophic cardiomyopathy, secondary forms of cardiomyopathy, stroke, peripheral artery disease, CKD. Informed consent was obtained from all study participants.

Echocardiography

The echocardiographic studies included two-dimensional, M-mode, pulsed Doppler and pulsed tissue Doppler imaging examinations and were performed with the use of a commercially available ultrasound system (Mindray echocardiography) by two expert cardiologists (G.M.R. and U.D.), who were blinded to patients' clinical information. Measurements were performed according to the American Society of Echocardiography guidelines [18]. Intra- and inter-observer variability, tested in 20% of unselected segments, was 3% and less than 5%, respectively.

LV volumes and EF were calculated from apical two- and four-chamber views using the modified Simpson's rule. LV mass was calculated and indexed for body surface area. Left atrial size and left atrial volume were also measured. The relative wall thickness was calculated as the ratio between posterior wall diastolic thickness multiplied by 2 and end-diastolic diameter. Midwall fractional shortening (MWFS) was calculated as previously described [19]. From the 4-chamber view, tissue Doppler longitudinal velocities were recorded with the sample volume placed at the junction between LV wall (medial and lateral) and the mitral annulus. The ratio of early transmitral flow to early diastolic mitral annular velocity (E/E') was then calculated at least in triplicate and then averaged.

Diastolic function grading was assigned based on the algorithm proposed in the 2016 Update of ASE/EACvi: averaged E/e' >14, septal e' velocity <7 cm/s or lateral e' velocity <10 cm/s, TR velocity >2.8 m/s, left atrial volume index >34 mL/m^2. Patients were classified as having LV diastolic dysfunction when they had >50% positive criteria [20].

Speckled tracking echocardiography was performed on three consecutive cardiac cycles of two-dimensional LV images from the three standard apical views. Custom acoustic tracking software allowing semi-automated, two-dimensionally derived strain analysis (EchoPAC Advanced Analysis Technologies; GE Healthcare) was applied to two-dimensional grayscale images by tracking movements of "speckles" in myocardial tissue, frame by frame, throughout the cardiac cycle. The software automatically divides each image into six myocardial segments and accepts segments of good tracking quality while rejecting poorly tracked segments, allowing the observer to manually override its decision at the same time using visual assessment. The peak negative systolic longitudinal strain was assessed from six segments in apical long-axis, four-chamber, and two-chamber view. GLS was calculated by averaging each value of regional peak longitudinal strain obtained in each apical view before aortic valve closure, which was defined in the apical long-axis view. Longitudinal strain was calculated by average of six basal, six middle, and six apical LV segments [21–23].

Less negative values reflect progressive impairment in GLS and therefore in LV systolic function. In HD patients, the echocardiographic study was performed in a mid-week interdialytic day.

Statistical Analysis

Data are shown as mean ± SD for continuous variables and as proportions for categorical variables. Normality of distributions was assessed using the Shapiro-Wilk test. Comparisons between continuous variables were analyzed by ANOVA and Kruskal-Wallis tests. Bonferroni test was used to compare single pairs of groups. The χ^2 test was used to compare categorical variables. Logistic regression was used to explore the determinants of LV systolic dysfunction. All variables showing a p value <0.1 at univariate analysis were tested in multivariable models. Stepwise procedure was used to build the multivariate models. The ability of the clinical and ultrasound variables to identify a compromised GLS was assessed by the receiver operator characteristic curve analysis. Data were analyzed using the IBM SPSS Software Package version 17.0.1.

Results

Table 1 shows demographic and clinical data of the 70 renal patients enrolled in the study compared to controls with or without hypertension. A compromised GLS <–18% was shown in 55% of patients with stage 2–4 CKD, 60% of HD, and 28% of KTRs, while it was 32% in

Table 1. Demographic, clinical, and echocardiographic variables in patients with renal disease, kidney transplant recipients, and controls with or without hypertension

Variable	CKD (n = 20) Group A	HD (n = 25) Group B	KTRs (n = 25) Group C	HTN (n = 50) Group D	Controls (n = 60) Group E	p value
Age, years	67±11$^{\times\#}$	58±13	52±14	56±11	53±10	<0.0001
% of women	25	36	32	54	52	0.076
Body mass index	28±4$^{\times\#}$	25±4	24±3	26±3	25±3	0.0005
Diabetes, %	55$^{\S\#}$	40§	24$^{\#}$	14	5	0.035
History of hypertension, %	90$^{\#}$	84$^{\#}$	80$^{\#}$	100$^{\#}$	0	<0.0001
Systolic blood pressure, mm Hg	149±18$^{\S\#}$	143±29*$^{\#}$	137±23$^{\#}$	134±16$^{\#}$	121±10	<0.0001
Diastolic blood pressure, mm Hg	74±13§	82±5*	75±11	84±7***$^{\#}$	78±6	0.0001
Heart rate, beats/min	70±10**	80±14$^{\S\#}$	72±13	70±12	71±15	0.032
LV end-diastolic volume, mL	98±18**	109±25*	93±22	102±20	102±28	0.051
LV end-systolic volume, mL	36±8	45±11$^{¤}$	38±11	40±11	39±123	0.0042
LV ejection fraction, %	60±3$^{\#}$	58±3*$^{\#}$	60±3$^{\#}$	61±5	63±5	0.0022
Left atrial volume, mL	36±11§§	48±28*$^{\#}$	32±15	47±13***	44±10	0.0002
RWT	0.46±0.09$^{\#}$	0.45±0.09$^{\#}$	0.42±0.07	0.43±0.05$^{\#}$	0.39±0.05	0.0002
LV mass, g	169±40**	226±78$^{\S\#}$	165±59	179±44$^{\#}$	153±58	<0.0001
LV mass index, g/m^2	91±20**	126±47$^{\S\#}$	90±29	98±21$^{\#}$	83±24	<0.0001
LV diastolic function, %	20	32$^{\#}$	12	24	5	0.0062
E/e'	9.7±2.9	11.3±3.4*$^{\#}$	9.7±3.0	11.0±2.6$^{\#}$	9.0±2.0	0.0003
MWFS, %	15.9±3.3	14.8±3.8***$^{\#}$	16.7±3.3	14.8±1.8***$^{\#}$	16.3±1.9	0.0043
GLS, %	–17.6±2.8$^{\#}$	–16.5±2.6*$^{\#}$	–18.3±4.5$^{\#}$	–18.6±3.5$^{\#}$	–20.8±3.1	<0.0001

CKD, chronic kidney disease; E/e', mitral E peak velocity and average ratio of mitral to myocardial early velocities; GLS, global longitudinal strain; HD, end-stage renal disease in hemodialysis; HTN, hypertensive patients; KTRs, kidney transplant recipients; LV, left ventricular; MWFS, midwall fractional shortening; RTW, relative wall thickness. $^{\times}$ $p < 0.05$ versus Groups B–D. $^{¤}$ $p < 0.05$ versus Groups A, C, D. § $p < 0.05$ versus Groups C, D. §§ $p < 0.05$ versus Groups B, D. $^{\#}$ $p < 0.05$ versus Group E. * $p < 0.05$ versus Group D. ** $p < 0.05$ versus Group B. *** $p < 0.05$ versus Group C.

Table 2. Predictors of GLS in patients with renal disease and kidney transplant recipients with normal ejection fraction by logistic regression analysis

Variable	Univariate		Multivariate	
	OR (95% CI)	p value	OR (95% CI)	p value
Age, years	1.03 (1.00–1.07)	0.067	1.02 (0.94–1.10)	0.63
Gender	1.90 (0.67–5.37)	0.22	5.22 (0.57–48.03)	0.14
Body mass index	1.10 (0.97–1.24)	0.12		
eGFR, mL/min/1.73 m^2	0.99 (0.97–1.00)	0.14		
Diabetes, %	2.87 (1.06–7.77)	0.038	2.00 (0.20–20.47)	0.56
History of hypertension, %	4.98 (0.99–25.05)	0.051	5.84 (0.20–173.39)	0.31
Systolic blood pressure, mm Hg	1.04 (1.01–1.06)	0.032	1.03 (0.97–1.09)	0.42
Diastolic blood pressure, mm Hg	1.03 (1.00–1.07)	0.093	1.02 (0.92–1.13)	0.69
Heart rate, beats/min	1.01 (0.97–1.04)	0.75		
LV ejection fraction, %	0.79 (0.66–0.95)	0.012	0.44 (0.08–2.53)	0.35
Left atrial volume, mL	1.08 (1.04–1.13)	0.0004	1.06 (0.98–1.14)	0.17
LV mass index, g/m^2	1.04 (1.02–1.06)	0.0007	1.07 (1.00–1.16)	0.063
E/e'	1.61 (1.26–2.05)	<0.0001	1.61 (1.06–2.44)	0.025
MWFS, %	0.78 (0.66–0.92)	0.0025	1.54 (0.86–2.78)	0.15

eGFR, estimated glomerular filtration rate; for other abbreviations see Table 1. Adjusted for: age, gender, BMI, eGFR, diabetes, history of hypertension, LV ejection fraction, systolic blood pressure, and diastolic blood pressure.

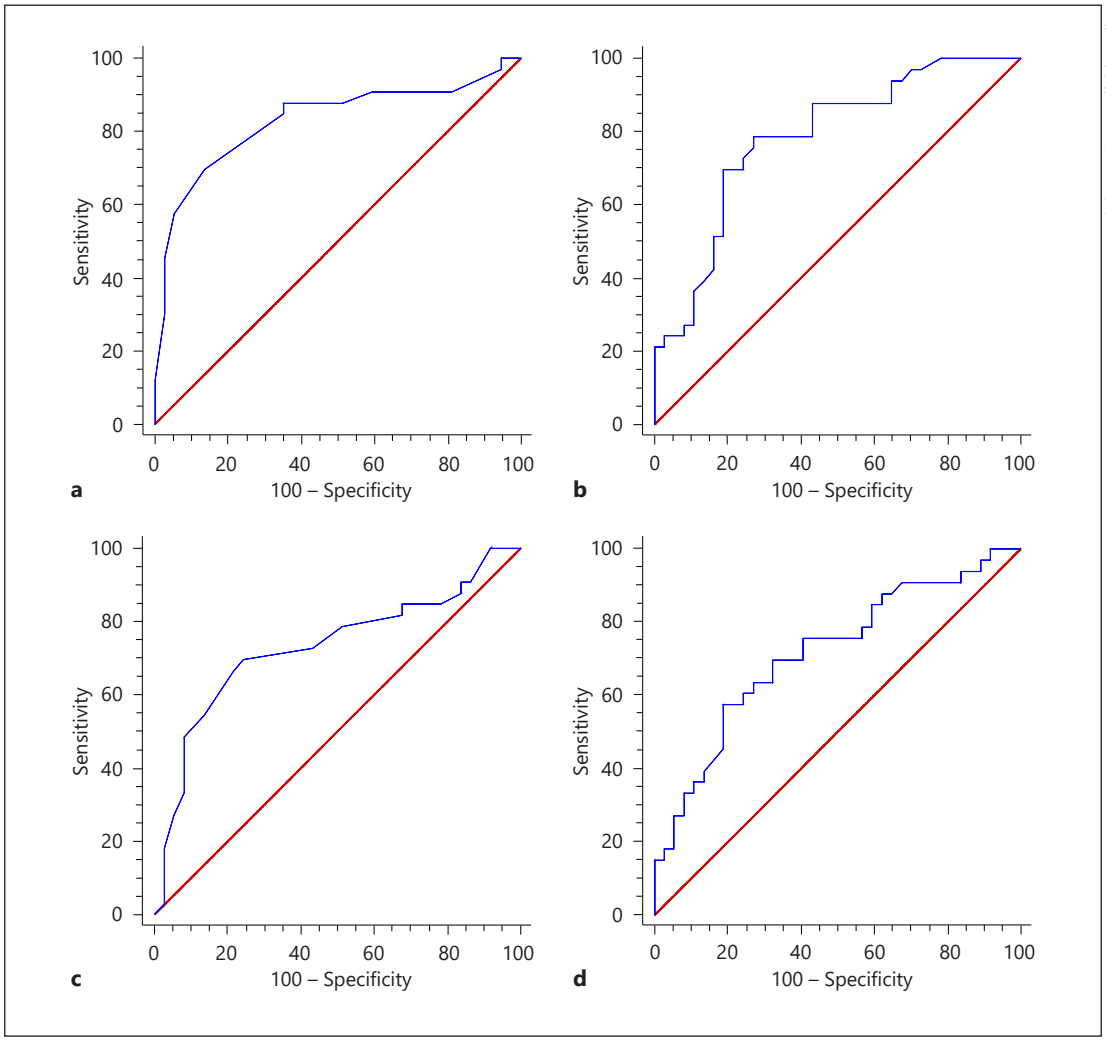

Fig. 1. The ability of different clinical and ultrasound parameters to predict a global longitudinal strain <–18% at the receiver operator characteristic curve analyses: E/e (**a**), LV mass (**b**), systolic blood pressure (**c**), and MWFS (**d**).

hypertensive controls and 12% in normotensive controls ($p < 0.0001$). Patients with renal disease (CKD and HD) were older, had higher systolic pressure, and a significantly greater prevalence of increased LV mass and diastolic dysfunction with respect to controls without hypertension. E/e' exhibited an area under the curve (AUC) of 0.83 (95% CI 0.72–0.91) for the identification of a GLS <–18% with a sensitivity of 70% and a specificity of 87%. LV mass exhibited an AUC of 0.78 (95% CI 0.67–0.87) with a sensitivity of 78% and a specificity of 72%, systolic blood pressure exhibited an AUC of 0.72 (95% CI 0.60–0.82) with a sensitivity of 70% and a specificity of 76%, and MWFS exhibited an AUC of 0.73 (95% CI 0.61–0.83) with a sensitivity of 58% and a specificity of 81% (Fig. 1). The estimated GFR showed an AUC of 0.56 (95% CI 0.44–0.68) with a sensitivity of 52% and a specificity of 68% for the prediction of compromised GLS.

Univariate and multivariate logistic regression analyses for the prediction of compromised GLS are shown in Table 2. E/e' ($p = 0.025$) and LV mass index ($p = 0.063$) were independently associated with a GLS <–18%.

Discussion

An important and novel finding of our study is that renal disease is associated with early and subclinical impairment of LV systolic function, as expressed by abnormal GLS, regardless of the degree of renal function worsening, and persisting even in spite of successful kidney transplantation. In our sample, although each patient had normal standard EF, less negative GLS values were demonstrated in both CKD and dialysis patients, and also in KTRs as compared with controls. Furthermore, no significant differences in GLS were observed when comparing CKD, dialysis, and transplanted patients. These findings are consistent with studies that showed less negative LV longitudinal strain in ESRD patients than in controls [10, 13, 24], but are at variance with a previous study that reported better GLS in ESRD patients on dialysis treatment than in those with CKD not requiring dialysis yet [25]. We have no reliable explanations of this discrepancy, since in both studies, volume status was similar in non-dialysis and dialysis patients, thus ruling out the occurrence of chronic fluid overload as the cause of worse GLS in the group of CKD patients not undergoing extracorporeal treatment. Interestingly, in our study, reduced subclinical LV systolic function is already present in early and moderate chronic renal disease and then persists in subjects who have reached the end stage.

Another relevant and novel finding of our study is that also KTRs had impairment of subclinical LV systolic function. Although available studies on GLS after transplantation are scant, improvement in subclinical LV systolic function is reported after successful kidney transplantation [26, 27]. Better LV strain was shown in KTRs evaluated by backscatter echocardiography [26] and more recently in 31 KTRs who underwent speckle echocardiography to assess their LV systolic function before and after grafting; however, the lack of a control group does not allow ascertaining whether GLS renormalized after kidney transplantation [27].

Considering the cross-sectional nature of our study, we could not assess changes in GLS after transplantation. However, the impaired GLS observed in our KTRs suggests that subclinical LV systolic dysfunction persists after transplantation, thus raising concerns over whether this abnormality may at least in part be related to the elevated morbidity and mortality still observed in KTRs [5, 28] and possibly supporting the notion that renal transplantation, even if associated with near complete restoration of kidney function, is the preferred treatment option for ESRD, but cannot be considered its cure [29].

In our cohort, MWFS was similar in renal patients and controls. Previous studies had shown reduced MWFS in CKD patients with preserved EF [30] and especially in those with end-stage kidney disease on dialysis, in whom progressively worsening fractional shortening was even significantly associated with adverse clinical outcome [4]. Taking into account that GLS resulted abnormal in subjects with all the stages of renal disease and also after transplantation, it is conceivable that GLS should be considered an earlier and more reliable index of future impairment of systolic function in the renal population than MWFS.

In our study, worsened GLS was strongly associated with LV hypertrophy and abnormal e/e' ratio, which even resulted the most powerful independent predictor of abnormal GLS. LV hypertrophy is one of the most important predictors of adverse CV and general outcome in renal patients [31] and is reportedly the strongest predictor of subsequent development of HF, both in early CKD and after kidney transplantation [3, 6]. Moreover, its regression was recently shown to be associated with better patient and graft survival in KTRs [32]. We cannot rule out that the reported association of LV hypertrophy with worse clinical outcome of renal patients could be at least in part related to the presence of subclinical LV systolic dysfunction in these patients. Interestingly, increased e/e' is a reliable and early marker of diastolic dysfunction, which is frequently observed in patients with renal disease [33], in whom it proved to be associated with poor CV outcome [34]. It is conceivable that early subclinical systolic and diastolic dysfunction coexist in renal disease, and probably this mutual rela-

tionship accounts for the high mortality and morbidity rate observed in renal patients, independent of disease stage, and even persisting after successful kidney transplantation.

Beyond the small sample size, the main limitation of our study, i.e., to be a single center study, is also its strength, since two experienced echocardiographists, blinded to the "renal" condition of enrolled subjects, evaluated their GLS. Moreover, this is the first study to evaluate at the same time patients with early CKD, those with ESRD, and KTRs, thus giving a comprehensive picture of the behavior of LV systolic function in the various stages of renal disease.

According to our findings, GLS as assessed by speckle echocardiography seems to be the better tool for ascertaining early and subclinical systolic LV dysfunction in renal patients. Moreover, renal disease per se proved to be associated with this impairment, which in fact persists after starting dialysis and even after kidney transplantation. Further interventional trials should be planned in order to evaluate the impact of treatment on this important abnormality of patients with renal disease, which probably is one of the causes of their persisting unfavorable CV outcome.

Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Disclosure Statement

The authors declare that they have no conflict of interest.

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