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ORIGINAL PAPER

LEFT VENTRICULAR FUNCTION IN PATIENTS WITH DIFFERENT STAGES OF CHRONIC KIDNEY DISEASE AND NO CARDIOVASCULAR DISEASE

Sergo KHAJALIA[1]✉, Zurab PAGAVA[1], Mikheil TSVERAVA[2], Rusudan AGLADZE[1], Tamar GAPRINDASHVILI[1], Tengiz VERULAVA[3]

[1] Department of Cardiology, Bokhua Memorial Cardiovascular Center, Tbilisi, Georgia
[2] Chapidze Cardiology Center, Tbilisi, Georgia
[3] School of Medicine, Caucasus University, Tbilisi, Georgia

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Abstract

Introduction. Cardiorenal syndrome (CRS) describes the bidirectional relationship between cardiac and renal dysfunction, often preceding clinical symptoms. The newer framework of Chronic Cardiovascular and Kidney Disorder (CCKD) expands on CRS by including subclinical dysfunction and shared pathophysiology.

The objective of the study was to assess early cardiac changes in asymptomatic chronic kidney disease (CKD) patients using global longitudinal strain (GLS) and measures of diastolic dysfunction.

Material and methods. We prospectively studied 78 CKD patients (stages 1–4) and 25 healthy controls. All participants underwent transthoracic echocardiography. Kidney function was evaluated using estimated glomerular filtration rate (eGFR), and correlations between echocardiographic parameters and eGFR were analyzed.

Results. Compared to controls, CKD patients exhibited significantly more structural heart changes and diastolic dysfunction (71.8% vs. 12%). Patients with

Résumé

Fonction ventriculaire gauche chez les patients présentant différents stades de maladie rénale chronique et aucune maladie cardiovasculaire

Introduction. Le syndrome cardiorénal (SCR) décrit la relation bidirectionnelle entre dysfonctionnements cardiaque et rénal, précédant souvent les symptômes cliniques. Le tout nouveau cadre de référence des maladies cardiovasculaires et rénales chroniques (MCRC) élargit le SCR en incluant les dysfonctionnements infracliniques et une physiopathologie commune.

L'objectif de cette étude était d'évaluer les changements cardiaques précoces chez les patients asymptomatiques atteints d'insuffisance rénale chronique (IRC) en utilisant la contrainte longitudinale globale (GLS) et des mesures de dysfonctionnement diastolique.

Materiel et méthodes. Nous avons étudié prospectivement 78 patients atteints d'IRC (stades 1 à 4) et 25 témoins sains. Tous les participants ont subi une échocardiographie transthoracique. La fonction rénale

✉ Address for correspondence: Sergo KHAJALIA
Department of Cardiology, Bokhua Memorial Cardiovascular Center, Tbilisi, Georgia
Address: 32-34 Erekle Tatishvili street, 7th floor
Email: S_khajalia@yahoo.com; Phone +995555588526

CKD stages 3–4 had reduced GLS and higher E/e' ratios than those with earlier-stage CKD. Correlation analysis revealed that lower eGFR was significantly associated with impaired GLS (r = –0.269, p = 0.017) and elevated E/e' (r = –0.288, p = 0.011), even in the absence of overt cardiovascular symptoms.

Conclusions. Declining renal function, as indicated by lower eGFR, is associated with subclinical cardiac changes, including impaired left ventricular global longitudinal strain (GLS) and elevated filling pressures. These findings highlight the potential of GLS and E/e′ ratio as early markers of cardiac dysfunction in CKD patients without overt cardiovascular disease, supporting the concept of cardiorenal syndrome within the CCKD framework.

Keywords: cardiorenal syndrome, heart-kidney interaction, speckle tracking echocardiography.

List of abbreviations:
CRS – cardiorenal syndrome
CCKD – chronic cardiovascular and kidney disorder
CKD – chronic kidney disease
GLS – global longitudinal strain
eGFR – estimated glomerular filtration rate
CVD – cardiovascular disease
BMI – body mass index
MDRD – the modification of diet in renal disease
LV- left ventricular
LVEF – left ventricular ejection fraction
E/e'- ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity

a été évaluée à l'aide du débit de filtration glomérulaire estimé (DFGe), et les corrélations entre les paramètres échocardiographiques et le DFGe ont été analysées.

Résultats. Comparativement aux témoins, les patients atteints d'IRC présentaient significativement plus de modifications cardiaques structurelles et de dysfonction diastolique (71,8% contre 12%). Les patients atteints d'IRC de stade 3 à 4 présentaient un GLS réduit et un rapport E/e' plus élevé que ceux atteints d'IRC à un stade plus précoce. L'analyse de corrélation a révélé qu'un DFGe plus faible était significativement associé à une altération du GLS (r = –0,269, p = 0,017) et à un E/e' élevé (r = –0,288, p = 0,011), même en l'absence de symptômes cardiovasculaires manifestes.

Conclusions. En conclusion, la diminution de la fonction rénale, indiquée par un DFGe plus faible, est associée à des modifications cardiaques infracliniques, notamment une altération de la déformation longitudinale globale (GLS) ventriculaire gauche et des pressions de remplissage élevées. Ces résultats soulignent le potentiel du GLS et du rapport E/e′ comme marqueurs précoces de dysfonctionnement cardiaque chez les patients atteints d'IRC sans maladie cardiovasculaire avérée, étayant ainsi le concept de syndrome cardiorénal dans le cadre de MCRC.

Mots-clés: syndrome cardiorénal, interaction cœur-rein, échocardiographie par suivi de speckle

Introduction

Nearly two centuries ago, in 1836, Robert Bright first demonstrated the significant interplay between the kidneys and the heart. Since that time, the scientific community has progressively focused on uncovering the underlying mechanisms of this bidirectional relationship, recognized in recent decades as cardiorenal syndrome (CRS)[1,2]. This connection emphasizes the importance of examining the kidneys and heart together, rather than separately, as each organ significantly affects the function of the other[2]. Chronic kidney disease (CKD) affects approximately 7% of the general population. Among individuals with CKD, the prevalence of cardiovascular disease (CVD) varies widely—from 7% to 85%—depending on the stage and type of kidney dysfunction. Furthermore, patients diagnosed with CKD are at a greater risk of dying from CVD than of progressing to the point of requiring renal replacement therapy[6].

Increasing awareness of the interconnected pathophysiology of metabolic, renal, and cardiovascular diseases has led to the concept of cardiovascular-kidney metabolic syndrome. This syndrome is a systemic disorder involving integrated metabolic, renal, and cardiovascular dysfunction, resulting in multiorgan impairment and elevated cardiovascular risk. The objective is to identify cardiovascular-kidney-metabolic syndrome at its earliest stages to prevent the progression to clinical cardiovascular disease and kidney failure[10,11].

In 2024, Zoccali and colleagues maintained that the term "cardiorenal syndrome" is outdated and recommended adopting the phrase "chronic cardiovascular and kidney disorder" (CCKD) instead. This conceptual framework is grounded in the shared risk factors and pathophysiological mechanisms between cardiovascular disease and chronic kidney disease. The initial manifestation of CCKD does not necessarily involve concurrent cardiac and renal failure and one organ may exhibit preserved function despite

underlying subclinical pathology[12]. Using the CCKD framework makes it possible to include both heart and kidney events together as combined outcomes in future research[13,14]. The "butterfly effect" deepens our understanding of CCKD by encompassing both its chronic aspects and the impact of acute organ insults that can lead to long-term, significant organ damage. The butterfly effect proposes that an acute, transient disturbance in one organ, such as the heart or kidneys, may precipitate long-term complications. This is especially important considering that, even after the affected organ has recovered, the initial insult may trigger pathological biological pathways that could ultimately lead to dysfunction in the other organ.

Fewer studies tested patients with CKD and asymptomatic from a cardiovascular standpoint using transthoracic echocardiography. In addition, global longitudinal strain (GLS) has been predominantly studied in patients with mild to moderate or moderate to severe CKD. Our study includes patients across all stages of CKD, with the exception of end-stage kidney disease.

The objective of the study was to determine whether any echocardiographic parameters are associated with declining kidney function.

Materials and methods

Study population

CKD patients were enrolled prospectively in Bokhua Memorial Cardiovascular Center between 2021 and 2024**.** Patients with known coronary artery disease, significant valvular heart disease, congenital heart disease, significant pericardial effusion or chronic constrictive pericarditis, irregular rhythms like atrial fibrillation or flutter, the poor window for echocardiography, patients on hemodialysis or peritoneal dialysis, pregnant patients, patients with morbid obesity (body mass index BMI ³ 30 kg/m^2), or mental problems were excluded from this study. We also recruited controls that had no known history of kidney or cardiovascular disease, or echocardiographic evidence of left ventricular systolic dysfunction.

The study was approved by the Research Ethics Committee of Caucasus University (CAU No. 012/22). The survey was conducted following the principle of informed consent. Respondents were provided with information about the study. There was also an examination of hospital documents on request and by doing so the responses have been validated.

Data collection

Using a structured questionnaire, anthropometric measurements, medical notes review, and current prescriptions, we captured data on CKD etiology, cardiovascular risk factors, and detailed drug history. All specimens for biochemical analysis were obtained on the day of the echocardiographic study, provided that there was no evidence of superimposed acute kidney injury during the time of blood sampling. The value of eGFR was calculated using the four-variable equation from the Modification of Diet in Renal Disease study (MDRD).

Echocardiographic assessment

Detailed echocardiographic evaluation was done using standard views including parasternal long axis and short axis view at three levels of the left ventricle and apical 4-, 3- and 2-chamber views. All echocardiographic studies were performed on the GE VIVID S60 2D echocardiographic system (GE healthcare, US) with 1.3–4.5 MHz 3Sc-RS adult probe. Echocardiographic images were stored for offline analysis. Left ventricular (LV) internal diameter during end diastole (LVEDD), right ventricular (RV) internal diameter during end diastole (RVEDD), interventricular septum diameter (IVSD), LV posterior wall thickness (LVPWT), values of left atrial (LA) and right atrial (RA) dimensions, sinus of Valsalva (SoV), ascending aorta (Asc AO), inferior vena cava (IVC), tricuspid annular plane systolic excursion (TAPSE), diastolic function, and left ventricular GLS were recorded. Left ventricle ejection fraction (LVEF) measurements were taken by using modified Simpson's biplane method. Diastolic dysfunction (DD) was assessed according guidelines.

Pulse-wave Doppler and tissue Doppler echocardiography

In the apical four chamber view, Doppler echocardiography was used to assess peak early diastolic transmitral velocity (E), peak late diastolic transmitral velocity (A), E/A ratio, and mitral E-wave deceleration time (DT). Tissue Doppler velocity analysis was done by placing a 2 mm Doppler sample in septal and lateral mitral annulus to measure septal and lateral peak early diastolic velocity (e'). E/e' was calculated as E divided by the mean of septal e' and lateral e'.

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 (IBM corp., USA). Continuous variables were tested for normality using the Kolmogorov–Smirnov test and those normally distributed were presented as mean ± standard deviation (SD), while those not following normal distribution were expressed as median and interquartile range (IQR). Categorical data were presented as frequency (n) and percentages (%). Comparison of proportions was performed using the

Table 1. Echocardiographic parameters in the study and control groups.

Variable	*Study group n=78*	*Control group n=25*	*Independent t-test*	*p-value*
	mean ± SD	*mean ± SD*		
LVEDd, mm	43.7±4.8	46.2±3.9	2.38	0.019*
RVEDd, mm	30.3±4.3	33.0±3.6	2.91	0.004*
LVEF, %	61.6±4.2	59.2±2.3	2.73	0.007*
IVSd, mm	12.0±2.6	8.4±1.6	6.57	<0.001*
LVPWT, mm	11.2±2.1	7.5±1.3	8.39	<0.001*
LA	37.8±4.1	31.2±4.6	6.67	<0.001*
RA	34.8±4.9	30.8±4.5	3.61	<0.001*
SoV	32.1±3.6	28.0±3.7	4.92	<0.001*
Asc AO	31.9±4.3	26.7±3.0	5.67	<0.001*
IVC	17.9±2.3	17.3±1.8	1.17	0.244
TAPSE	22.7±4.6	23.3±2.1	0.64	0.525
E	0.67±0.20	0.78±0.13	2.58	0.011*
A	0.80±0.19	0.60±0.14	4.74	<0.001*
E/e'	8.9±2.3	8.6±1.6	0.54	0.592
GLS, %	-18.0±3.3	-19.0±1.9	1.67	0.098

* p<0.05; A, apical peak late diastolic transmitral velocity; Ascending AO, ascending aorta; E- apical peak early diastolic transmitral velocity; E/e'-apical peak early diastolic transmitral velocity /mean peak early diastolic velocity; GLS – global longitudinal strain; IVC – inferior vena cava; IVSD – interventricular septum diameter; LA – left atrium; LVEDD – left ventricular internal diameter during end diastole; LVEF – left ventricular ejection fraction; LVPWT – left ventricular posterior wall thickness; RA – right atrium; RVEDD – right ventricular internal diameter during end diastole; SoV – sinus of Valsalva; TAPSE – tricuspid annular plane systolic excursion.

Table 2. Echocardiographic parameters in the study subgroups.

Variable	*Study subgroup1 n=23*	*Study subgroup2 n=55*	*Independent t-test*	*p-value*
	mean ± SD	*mean ± SD*		
eGFR, mL/min/1.73m^2	42.2±14.6	74.9±8.7	12.25	<0.001*
LVEDd, mm	45.2±5.1	43.0±4.5	1.89	0.062
RVEDd, mm	32.0±5.3	29.6±3.7	2.30	0.024*
LVEF, %	60.0±3.6	62.3±4.3	2.31	0.024*
IVSd, mm	12.8±2.9	11.6±2.4	1.94	0.056
LVPWT, mm	11.7±2.1	11.0±2.0	1.32	0.190
LA	39.1±4.1	37.2±4.1	1.86	0.066
RA	35.8±4.7	34.3±4.9	1.26	0.210
SoV	32.2±3.4	32.1±3.7	0.14	0.888
Asc AO	32.7±3.9	31.6±4.4	0.99	0.325
IVC	18.3±2.9	17.7±2.0	0.96	0.340
TAPSE	21.3±3.8	23.2±4.9	1.69	0.094
E	0.65±0.20	0.68±0.20	0.59	0.557
A	0.79±0.17	0.81±0.21	0.34	0.738
E/e'	9.9±2.8	8.5±2.0	2.41	0.018*
GLS, %	-16.6±3.8	-18.6±2.8	2.65	0.010*

* p<0.05; A, apical peak late diastolic transmitral velocity; Ascending AO, ascending aorta; E- apical peak early diastolic transmitral velocity; E/e'- apical peak early diastolic transmitral velocity /mean peak early diastolic velocity; GLS – global longitudinal strain; IVC – inferior vena cava; IVSD – interventricular septum diameter; LA – left atrium; LVEDD – left ventricular internal diameter during end diastole; LVEF – left ventricular ejection fraction; LVPWT – left ventricular posterior wall thickness; RA – right atrium; RVEDD – right ventricular internal diameter during end diastole; SoV – sinus of Valsalva; TAPSE – tricuspid annular plane systolic excursion.

Table 3. Echocardiographic parameters in study subgroups.

eGFR vs.	*Pearson coefficient (r)*	*p-value*
LVEDd, mm	-0.163	0.153
RVEDd, mm	0.189	0.098
LVEF, %	-0.229	0.044*
IVSd, mm	-0.155	0.176
LVPWT, mm	-0.108	0.466
LA	-0.176	0.123
RA	-0.109	0.342
SoV	0.034	0.769
Asc AO	-0.106	0.353
IVC	-0.116	0.313
TAPSE	0.158	0.168
E	0.115	0.640
A	-0.025	0.902
E/e'	-0.288	0.011*
GLS, %	-0.269	0.017*

* p<0.05; A, apical peak late diastolic transmitral velocity; Ascending AO, ascending aorta; E – apical peak early diastolic transmitral velocity; E/e'- apical peak early diastolic transmitral velocity /mean peak early diastolic velocity; GLS – global longitudinal strain; IVC – inferior vena cava; IVSD – interventricular septum diameter; LA – left atrium; LVEDD – left ventricular internal diameter during end diastole; LVEF – left ventricular ejection fraction; LVPWT – left ventricular posterior wall thickness; RA – right atrium; RVEDD – right ventricular internal diameter during end diastole; SoV – sinus of Valsalva; TAPSE – tricuspid annular plane systolic excursion.

chi-squared test and normally distributed continuous data were compared using the independent t-test. Mann–Whitney U test was used to compare non-normal continuous data. Correlation analysis between variables was performed by Pearson coefficient (r). All results were considered significant at a p-value < 0.05.

Results

A total of 78 patients with CKD stages 1–4 were selected in the study group after obtaining written consent. The mean age of the study group participants was 60.9±15.2 years; male/female ratio of study group was 23/55 (29.5%/70.5%). The mean value of eGFR was 60.9±15.1 mL/min/1.73m^2 (min/max, 15.0–90.0; median 68.0). A total of 25 persons were enrolled in the control group after obtaining the written consent. CKD stage 1 was diagnosed in one patient (1.3%), CKD stage 2 in 54 patients (69.2%), CKD stage 3a in 12 patients (15.4%), CKD stage 3b in 5 patients (6.4%), and CKD stage 4 in 6 patients (7.7%). Therefore, the study group was divided into two subgroups: subgroup 1 – patients with CKD 3-4 (n=23), and subgroup 1 – patients with CKD 1-2 (n=55).

The mean age of the controls was 57.2±10.1 years; male/female ratio of study group was 14/11 (56.0%/44.0%). The mean value of eGFR was 101.1±6.9 mL/min/1.73m^2 (min/max, 92.0–114.0, median 99.0).

The echocardiographic parameters obtained in the study and control groups are presented in Table 1. All echocardiographic parameters (except inferior vena cava, tricuspid annular plane systolic excursion, E/e', and GLS, %) were significantly different between the study and control groups.

The echocardiographic parameters obtained in the study subgroups are presented in Table 2.

RVEDd, LVEF, E/e', and GLS mean values were significantly higher in the group of patients with CKD 3-4 compared to the patients with CKD 1-2. Diastolic dysfunction in subgroup 1 was identified in 87.0% of patients: grade 1 in 69.6%, and grade 2 in 17.4%. Therefore, diastolic dysfunction grade 1 was identified in 56 patients (71.8%) of the study group, and in three patients (12.0%) of the control group.

The correlations between eGFR and the echocardiographic parameters obtained in the study group are presented in Table 3. Correlation analysis showed that eGFR was significantly negatively associated with LVEF (r = –0.229, p=0.044), E/e' (r= – 0.288, p=0.011), and GLS (r = –0.269, p=0.017).

Discussion

The present study demonstrated that eGFR was negatively correlated with left ventricular GLS and filling pressure in asymptomatic (from the cardiovascular point of view) patients. Moreover, mean GLS values were significantly higher in patients with CKD stages 3-4 compared to those with CKD stages 1-2.

Left ventricular systolic dysfunction in patients with CKD is multifactorial, with pressure and volume overload serving as primary hemodynamic stressors that contribute to impaired contractile performance. Chronic inflammation and oxidative stress, both prevalent in CKD, promote interstitial fibrosis and adverse ventricular remodeling. Additional contributors include uremic toxins and anemia, which exacerbate myocardial strain and compromise systolic function through increased metabolic demand and direct cardiotoxic effects. Most studies evaluating GLS in patients without established cardiovascular disease were conducted in individuals with mild to moderate or moderate to severe CKD[15,16,18,19]. A key strength of our study is the inclusion of CKD patients from stages 1 to 4. We demonstrated a negative correlation between eGFR and left ventricular GLS in the study group. This fact can suggest that declining kidney function is associated with subclinical myocardial dysfunction, independent of overt cardiovascular disease. This finding may imply that left ventricular GLS assessment should be performed in CKD patients with risk factors but without established cardiovascular disease.

Our study found that LV hypertrophy is inherent in CKD patients compared to healthy control group. Similar results were obtained by other authors and this association was more pronounced in late stages of disease[27,28]. Patients with left ventricular hypertrophy can be asymptomatic for years, but progression of disease will eventually result in development of heart failure. On the other hand, a thickened left ventricle disturbs normal conduction, and the risk of arrhythmias increases. This finding suggests that in patients with CKD all factors that contribute to the progression of LV hypertrophy must be controlled, with a strict blood pressure control and active encouragement of healthy lifestyle.

Diastolic dysfunction is common in CKD patients and has been reported both in patients with end-stage renal disease on dialysis and in patients with CKD not on dialysis. One method used to evaluate diastolic function is to estimate left ventricular filling pressure and it can be reliably calculated with the ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e'). We found a negative correlation between GFR and E/e' ratio. Increased peak E velocity can be explained by augmented sodium and fluid retention in CKD; the presence of LV hypertrophy, on the other hand, leads to delayed relaxation, impaired LV compliance and consequently, a reduced e' velocity. This result is in line with other studies, but these studies enrolled patients with moderate to severe CKD; our group included patients with all stages of chronic kidney impairment. Sulemane et al. revealed that E/e' independently predicted major adverse cardiovascular events in CKD patients with diastolic dysfunction[28]. In another study, exercise E/e' was identified as the most significant predictor of exercise capacity and was found to be a valuable tool for improving the detection of latent diastolic dysfunction in patients with stage 3 and 4 CKD[29].

Our research showed that in patients with CKD and no cardiovascular disease some echocardiographic parameters might have more significance. This relates to such measurements as left ventricular GLS or the E/e' ratio. In addition, we assume that the assessment of left ventricular GLS in the early stages of CKD enables the identification of subclinical systolic dysfunction in a greater proportion of patients compared to conventional measures such as LVEF.

Limitations. This study has several limitations. First, the sample size was relatively modest, which may limit the generalizability of the findings. Second, the urine albumin-to-creatinine ratio was not assessed in the study population. Additionally, GLS analysis of the right ventricle was not conducted.

Conclusions

The findings of this study suggest that declining renal function, as indicated by lower eGFR, is associated with subclinical alterations in cardiac mechanics, including impaired left ventricular GLS and elevated filling pressure, even in asymptomatic individuals. A key contribution of this study lies in its focus on a relatively understudied population, as limited research has examined echocardiographic parameters in patients with CKD stages 1–4 in the absence of overt cardiovascular disease. As right ventricular GLS was not assessed in the present study, future research should include its evaluation to provide a more comprehensive assessment of cardiac function. Our results may imply that left ventricular GLS and the E/e′ ratio represent early indicators of cardiac dysfunction in patients with CKD and in the absence of overt cardiovascular disease.

Author Contributions:

Conceptualization, S.K., Z.P., M.T., R.A., T.G. T.V.; *methodology,* S.K., Z.P., M.T., R.A., T.G.; *software,* S.K., Z.P., R.A., T.G.; *validation,* S.K., Z.P., M.T., R.A., T.V.; *formal analysis,* S.K., Z.P., M.T., R.A., T.G.; *investigation,* S.K., Z.P., M.T., R.A., T.G.; *resources,* S.K., Z.P., M.T., R.A., T.G.; *data curation,* S.K., Z.P., R.A., T.G. T.V.; *writing–original draft preparation,* S.K., Z.P., M.T., R.A., T.G.; *writing–review and editing,* S.K., Z.P., M.T., R.A., T.G. T.V.; *visualization,* S.K., M.T., R.A., T.G. T.V.; *supervision,* S.K., Z.P., M.T., R.A., T.V.; *project administration,* S.K., R.A., T.G. T.V. *All the authors have read and agreed with the final version of the article.*

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article".

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2000(5), as well as the national law. Informed consent was obtained from all the patients included in the study".

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