Kidney Diseases

Research Article

Kidney Dis
DOI: 10.1159/000529526

Received: October 15, 2022
Accepted: January 30, 2023
Published online: February 13, 2023

Defining Biventricular Abnormalities by Cardiac Magnetic Resonance in Pre-Dialysis Patients with Chronic Kidney Disease

Li Qi[a] Beibei Zhi[a] Jun Zhang[a] Lingyan Zhang[a] Song Luo[b] Longjiang Zhang[a, b]

[a]Department of Radiology, Jinling Hospital, Nanjing Medical University, Nanjing, China; [b]Department of Radiology, Jinling Hospital, Medical School of Nanjing University, Nanjing, China

Keywords
Cardiac magnetic resonance · Chronic kidney disease · Left ventricle · Right ventricle

Abstract
Introduction: The aim of the study was to investigate biventricular structural and functional abnormalities in pre-dialysis patients across stages of chronic kidney disease (CKD) by cardiac magnetic resonance (CMR). ***Methods:*** Fifty-one CKD patients with CMR exams were retrospectively analyzed. Patients were divided into three groups according to estimated glomerular filtration rate (eGFR): CKD 1 group (patients with normal eGFR≥90 mL/min/1.73 m^2, $n = 20$), CKD 2-3 group (patients with eGFR< 90 to ≥30 mL/min/1.73 m^2, $n = 14$), and CKD 4-5 group (patients with eGFR<30 mL/min/1.73 m^2, $n = 17$). Twenty-one age- and sex-matched healthy controls (HC) were recruited. CMR-derived left ventricular (LV) and right ventricular (RV) structural and functional measures were compared. Association between CMR parameters and clinical measures was assessed. ***Results:*** There was an increasing trend in RV mass index (RVMi) and LV mass index (LVMi) with the occurrence and development of CKD from HC group to CKD 4-5 group although no significant difference was observed between CKD 1 group and HC group. LV global radial strain and LV global circumferential strain dropped and native T1 value elevated significantly in CKD 4-5 group compared with the other three groups (all $p < 0.05$), while RV strain measures, RV ejection fraction, and LV ejection fraction showed no significant difference among 4 groups (all $p > 0.05$). Elevated LV end-diastolic volume index ($\beta = 0.356$, $p = 0.016$) and RV end-systolic volume index ($\beta = 0.488$, $p = 0.001$) were independently associated with RVMi. Increased systolic blood pressure ($\beta = 0.309$, $p = 0.004$), LV end-systolic volume index ($\beta = 0.633$, $p < 0.001$), and uric acid ($\beta = 0.261$, $p = 0.013$) were independently associated with LVMi. Meanwhile, serum phosphorus ($\beta = 0.519$, $p = 0.001$) was independently associated with native T1 value. ***Conclusion:*** In pre-dialysis CKD patients, left and right ventricular remolding has occurred. RVMi and LVMi were the first changed CMR indexes in the development of CKD when eGFR began to drop. Because fluid volume overload was the independent risk factor for RVMi and LVMi increase, reasonable controlling fluid volume overload may slow down the progression of biventricular remolding and may reduce related cardiovascular disease risk.

Drs. Li Qi and Beibei Zhi had equal contributions to this work as co-first authors.
Drs. Zhang and Luo had equal contributions to this work as co-corresponding authors. Dr. Zhang contributed to the conception of the study and writing – review and editing, and Dr. Luo contributed to the conception of the study.

karger@karger.com
www.karger.com/kdd

Correspondence to:
Long Jiang Zhang, kevinzhlj@163.com
Song Luo, hnldls@163.com

Introduction

Chronic kidney disease (CKD) is associated with diverse subtypes of cardiovascular diseases (CVDs), dominating with cardiac diseases such as coronary artery disease, heart failure, arrhythmias, and sudden cardiac death [1, 2]. Indeed, patients with CKD are more likely to develop a cardiovascular event than to progress to end-stage kidney disease requiring renal replacement therapy [3]. The reasons for the elevated CVD risk are complex and not completely understood, which are suggested in part to be attributed to the structural and functional changes of the myocardium [4].

Cardiac structure and function changes have been found to be related to the prognosis of multifarious cardiopulmonary diseases such as pulmonary hypertension, left heart diseases, tricuspid regurgitation, and cardiomyopathies [5–8]. In CKD patients, left ventricular (LV) remodeling and right ventricular (RV) dysfunction were also verified to be associated with adverse cardiovascular outcomes and total mortality [9–12]. However, most previous studies focused on dialysis CKD patients because of the more pronounced changes in biventricular structure and function caused by dialysis. Actually, cardiac structure and function have been changed in pre-dialysis patients since the deleterious effects driven by CKD on the cardiovascular system were already at work. Thus, assessment of the early cardiovascular damage and risk conferred by CKD in the early stages is of pivotal importance in prevention of major cardiovascular events.

Cardiac magnetic resonance (CMR) has been established as the most accurate noninvasive method to assess structure and function of left ventricle and right ventricle with a significantly lower interobserver variability compared to echocardiography [13, 14]. In recent years, the development of some advanced CMR technologies, such as feature tracking and T1 mapping, makes CMR not only characterize cardiac volumes but also assess the properties and consequential pathology of myocardial tissue [15]. A few studies have shown significant differences in these LV CMR parameters between CKD patients and healthy controls (HCs), indicating CMR values could be considered as subclinical indicators in exploring LV structural and functional abnormalities [16, 17]. However, structural and functional abnormality of right ventricle has not been studied in pre-dialysis patients by CMR. More importantly, it is urgently needed to explore the change pattern of biventricular CMR parameters to find the most sensitive index that may help detect early myocardium abnormality and guide clinical interventions in CKD patients. Therefore, the aims of our study were to assess biventricular abnormalities in pre-dialysis CKD patients and to identify the structural and functional change pattern using multiparametric CMR.

Materials and Methods

Study Population

This is a retrospective study that included pre-dialysis CKD patients undergoing CMR examination from July 2015 to March 2022 at Jinling hospital. Inclusion criteria were established diagnosis of CKD with a stage of 1-5 without dialysis by nephrologists according to the 2012 KDIGO guidelines [18] and age more than 18 years old. Exclusion criteria were renal etiologies that may cause cardiac structure and function abnormality (such as diabetes mellitus [n = 13], hypertensive nephropathy [n = 3], renal amyloidosis [n = 2], lupus nephritis [n = 6], ANCA-associated vasculitis [n = 2]), known coronary artery disease (angina, myocardial infarction, prior percutaneous or surgical revascularization), moderate or severe valvular heart disease, the loss of image data (n = 3), inadequate image quality for CMR analysis owing to artifacts (n = 4), and unexplained outcomes (n = 2). Finally, a total of 51 patients were enrolled in this study. Based on estimated glomerular filtration rate (eGFR) calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [19], the patients were divided into three groups: CKD 1 group, patients with normal eGFR ≥90 mL/min/1.73 m^2; CKD 2-3 group, patients with eGFR <90 to ≥30 mL/min/1.73 m^2; CKD 4-5 group, patients with eGFR <30 mL/min/1.73 m^2. In addition, 21 age- and sex-matched HCs without any history or symptoms of CKD or other chronic disease were recruited. Demographic, blood, and proteinuria data were collected from all subjects. Laboratory results were captured within 7 days before and after CMR. This study was approved by the Institutional Review Board of Jinling hospital (2015NZGKJ-085) and written informed consent was waived from all the participants.

CMR Imaging

All CMR studies were performed at 3-Tesla scanner (Trio; Siemens Medical Solutions, Erlangen, Germany) with a 6-channel cardiac coil for acquisition of cardiac function, volumes, mass, myocardial native T1 mapping. Cine images of 4-chamber and short-axis views were acquired with electrocardiogram-gated breath-hold balanced steady-state free precession sequence covering the entire left and right ventricles. The acquisition parameters for short-axis views were as follows: time of repetition (TR) = 50.85 ms, time of echo (TE) = 1.5 ms, flip angle = 50°, matrix size = 256 × 179 mm^2, slice thickness = 8 mm, voxel size = 1.9 × 1.3 × 8 mm, field of view (FOV) = 340 × 340 mm^2, temporal resolution = 24.70 ms. The acquisition parameters for 4-chamber views were TR = 40.80 ms, TE = 1.50 ms, flip angle = 50°, matrix size = 256 × 256 mm^2, slice thickness = 6 mm, voxel size = 2.4 × 1.8 × 8 mm, FOV = 340 × 340 mm^2, temporal resolution = 24.40 ms. Typically, 25 phases were acquired per cardiac cycle in both 4-chamber long-axis cine images and short-axis cine images. Native T1 mapping was performed with breath hold at end-expiration using the modified look-locker inversion-recovery sequence with a 5(3)3 sampling protocol at a basal, a mid-ventricular, and an apical LV short-axis slice. The acquisition parameters were TE = 1.12 ms; TR = 314.85 ms; flip angle = 35°; matrix size = 256 × 169 mm^2; slice thickness = 8 mm; voxel size = 2.1 × 1.4 × 8.0 mm^3; FOV = 360 × 360 mm^2.

Table 1. Demographic data and subject characteristics in HC group and CKD groups

Variables	HCs (n = 21)	CKD 1 (eGFR ≥90 mL/min/1.73 m^2) (n = 20)	CKD 2-3 (30 ≤ eGFR <90 mL/min/1.73 m^2) (n = 14)	CKD 4-5 (eGFR <30 mL/min/1.73 m^2) (n = 17)	p value
Male, n (%)	9 (42.90%)	9 (45.00%)	8 (57.10%)	8 (47.10%)	0.861
Age, years	42±12	40±13	44±9	46±10	0.284
BMI, kg/m^2	22.8±2.95	25.2±4.2	23.3±3.6	21.6±2.3	0.017
HR, beats/min	69 (62.5, 80.5)	76.5±10.7	70.4±12.0	77.0±9.6	0.109
SBP, mm Hg	NA	129.5±16.5	124.7±15.3	144.3±16.9	0.005
DBP, mm Hg	NA	81.7±10.4	82.9±10.9	92.3±9.4	0.010
Duration of CKD, median, months	NA	2.92 (1.5, 13.6)	3.05 (0.8, 29.7)	75.47 (13.9, 102.4)	0.016
Etiology, n (%)					
Glomerulonephritis	NA	20 (100%)	10 (71.4%)	7 (41.2%)	<0.001
Gout	NA	0	1 (7.1%)	0	
Other/unknown	NA	0	3 (21.4%)	10 (58.8%)	
Drugs					
ACEi/ARB	NA	5 (25%)	6 (42.9%)	10 (58.8%)	0.051
Beta-blocker	NA	1 (5%)	1 (7.1%)	8 (47.1%)	0.065
Statin	NA	6 (30%)	0	2 (11.8%)	0.001
Laboratory results					
Blood hemoglobin, g/L	NA	130.7±19.2	128.6±17.3	93.9±18.4	<0.001
Blood hematocrit, %	NA	0.4±0.1	0.4±0.1	0.3±0.1	<0.001
Serum uric acid, μmol/L	NA	354.9±101.1	443.2±95.7	450.8±115.5	0.014
Serum phosphorus, mmol/L	NA	1.1±0.2	1.2±0.2	1.9±0.6	<0.001
Serum calcium, mmol/L	NA	2.1±0.2	2.1±0.1	2.1±0.2	0.787
Glucose, mmol/L	NA	5.4±0.6	5.0±0.6	5.8±0.8	0.016
eGFR, mL/min/1.73 m^2	NA	114.3 (98.5, 124.1)	68.8±20.0	7.0 (5.0, 11.0)	<0.001
24-h urinary protein, g/d	NA	2.8±2.0	2.8 (1.6, 5.4)	1.83 (1.1, 2.9)	0.372

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; HR, heart rate.

Post-Processing Analysis

All CMR images were analyzed with CVi42 (version 5.13.5, Circle Cardiovascular Imaging, Calgary, Canada) software by an experienced cardiovascular radiologist with 5 years of experience in CMR blinded to all clinical data. In order to assess interobserver consistency for the analysis of all CMR parameters, 21 anonymized subjects were measured independently by another blinded reader with 8 years of experience in CMR.

Analysis of RV and LV Function

LV and RV endocardial and epicardial contours on short-axis cine images were drawn in end-diastole and end-systole images, excluding trabeculations and papillary muscles in the blood pool. Then, biventricular function and volume parameters were derived, including end-diastolic volume index, end-systolic volume index, systolic volume index, mass index, and ejection fraction.

Analysis of Strain

In the end-diastolic frame, endocardial and epicardial borders in LV and RV short-axis images and 4-chamber long-axis images were drawn and automatically tracked throughout the cardiac cycle to obtain biventricular strain parameters, including global radial peak strain, global circumferential peak strain, and global longitudinal strain.

Analysis of Native T1 Mapping

For analysis of LV native T1 mapping, endocardial and epicardial borders were manually drawn in the basal, mid-ventricular, and apical regions short-axis slices avoiding blood pool and epicardial fat contamination.

Statistical Analysis

Statistical analysis was performed using SPSS version 23.0 (SPSS Inc., IBM Corporation, Armonk, NY, USA). Normality was assessed using the Shapiro-Wilk test. Continuous variables were reported as means and standard deviations when they were normally distributed and as medians and interquartile ranges when non-normally distributed. Categorical variables were presented as frequencies with percentages. Comparisons were carried out with one-way ANOVA (post hoc tests: least significance difference) for normally distributed continuous variables and Kruskal-Wallis tests for non-normally distributed variables. The χ^2 test or Fisher's exact test were used for categorical variables. Parameters with p value <0.1 at univariate analysis were included in multivariable analysis with stepwise model to determine the independent association between baseline parameters and CMR indices. There was no multicollinearity between variables in the multivariate model. Interobserver reproducibility was assessed by using intra-class correlation coefficients (ICCs) with two-way mixed model and consistency type. Reproducibility was

Table 2. LV and RV structural and functional parameters on CMR

Variables	HCs (n = 21)	CKD 1 (eGFR ≥90 mL/min/1.73 m^2) (n = 20)	CKD 2–3 (30 ≤ eGFR <90 mL/min/1.73 m^2) (n = 14)	CKD 4–5 (eGFR <30 mL/min/1.73 m^2) (n = 17)	p value
LVEDVi, mL/m^2	67.8±7.0*	67.3±17.1[b]	70.9±14.5[c]	86.8±19.9	0.001
LVESVi, mL/m^2	26.0±4.1*	26.7±8.4[b]	29.0±10.7[c]	37.5±11.1	0.001
LVSVi, mL/m^2	41.8±5.1*	40.6±10.3[b]	42.0±6.5[c]	49.3±10.5	0.013
LVEF, %	61.7±4.4*	60.7±5.6	60.1±7.1	57.3±5.4	0.102
LVMi, g/m^2	40.9±6.7[a*]	46.5±9.5[b]	48.1±12.3[c]	59.9±8.2	<0.001
Male	44.7±6.6*	53.5±8.8	50.2±15.8[c]	61.1±9.1	0.024
Femal	38.1±5.5[a*]	40.7±5.2[b]	45.4±5.3[c]	58.9±7.7	<0.001
RVEDVi, mL/m^2	67.6±10.1*	66.9±13.0[b]	73.8±12.6	79.2±18.3	0.027
RVESVi, mL/m^2	32.4±8.2	32.5±9.4	35.6±9.7	38.4±14.1	0.262
RVSVi, mL/m^2	35.2±6.0*	34.4±7.4[b]	38.2±7.3	40.8±8.7	0.043
RVEF, %	52.4±7.6	51.5±8.3	52.1±7.9	52.5±8.8	0.980
RVMi, g/m^2	10.4±1.2[a*]	11.1±2.0	12.2±2.2	12.2±2.2	0.014
Male	10.7±1.4	12.1±2.1	13.0±2.1	12.9±2.5	0.088
Female	10.2±1.1	10.4±1.8	11.2±2.0	11.5±1.7	0.260
LVGRS, %	34.4±5.5*	33.7±6.5[b]	33.7±7.1[c]	29.1±5.0	0.044
LVGCS, %	−19.6±1.9*	−19.3±2.3[b]	−19.3±2.6[c]	−17.6±1.9	0.035
LVGLS, %	−17.6±2.4	−17.1±2.6	−17.9±3.6	−17.1±2.1	0.777
RVGRS, %	28.1±9.4	27.0±8.6	28.2±8.6	29.5±8.6	0.884
RVGCS, %	−15.4±4.5	−15.1±3.5	−15.6±3.4	−15.4±3.4	0.989
RVGLS, %	−20.3±9.9	−21.2±5.2	−21.5±5.6	−20.7±5.7	0.962
Native T1, ms	1,240.6±56.6*	1,233.7±50.3[b]	1,244.4±71.8[c]	1,303.9±70.5	0.004

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVSVi, left ventricular stroke volume index; LVMi, left ventricular mass index; LVEF, left ventricular ejection fraction; RVEDVi, right ventricular end-diastolic volume index; RVESVi, right ventricular end-systolic volume index; RVSVi, right ventricular stroke volume index; RVEF, right ventricular ejection fraction; LVGRS, left ventricular global radial strain; LVGCS, left ventricular global circumferential strain; LVGLS, left ventricular global longitudinal strain; RVGRS, right ventricular global radial strain; RVGCS, right ventricular global circumferential strain; RVGLS, right ventricular global longitudinal strain. *p < 0.05 versus HCs and CKD 4-5 patients with eGFR < 30 mL/min/1.73 m^2. [a]p < 0.05 versus HCs and CKD 2-3 patients with eGFR ≥ 30 mL/min/1.73 m^2. [b]p value versus CKD 1 patients with eGFR ≥ 90 mL/min/1.73 m^2 and CKD 4-5 patients with eGFR < 30 mL/min/1.73 m^2. [c]p value versus CKD 2-3 patients with eGFR ≥ 30 mL/min/1.73 m^2 and CKD 4-5 patients with eGFR < 30 mL/min/1.73 m^2.

defined as poor (ICC <0.5), moderate (0.5 ≤ ICC <0.75), good (0.75 ≤ ICC <0.9), or excellent (ICC ≥0.9) [20]. A two-sided p < 0.05 was considered statistically significant.

Results

Subject Characteristics

Baseline demographic and laboratory characteristics for all included subjects are summarized in Table 1. Sex, age, and heart rate were not significantly different among 4 groups, while there was a significantly progressive deterioration in systolic blood pressure (SBP), diastolic BP, glucose, serum phosphorus, serum uric acid, hemoglobin, and hematocrit with the decrease of eGFR.

CMR Parameters

The comparisons of CMR parameters among the four groups are summarized in Table 2. In terms of changes in biventricular structure, there was an increasing trend in RVMi and LVMi with the occurrence and development of CKD from HC group to CKD 4-5 group although no significant difference was observed between CKD 1 group and HC group. The same trend was shown when RVMi and LVMi were compared based on gender although no significant difference was observed for RVMi due to the small sample size. In terms of changes in biventricular function, LVGRS and LVGCS dropped significantly in CKD 4-5 group compared with the other three groups (all p < 0.05), while RV strain measures showed no significant difference among 4 groups (all p > 0.05). RVEF and LVEF showed no significant difference among 4 groups although

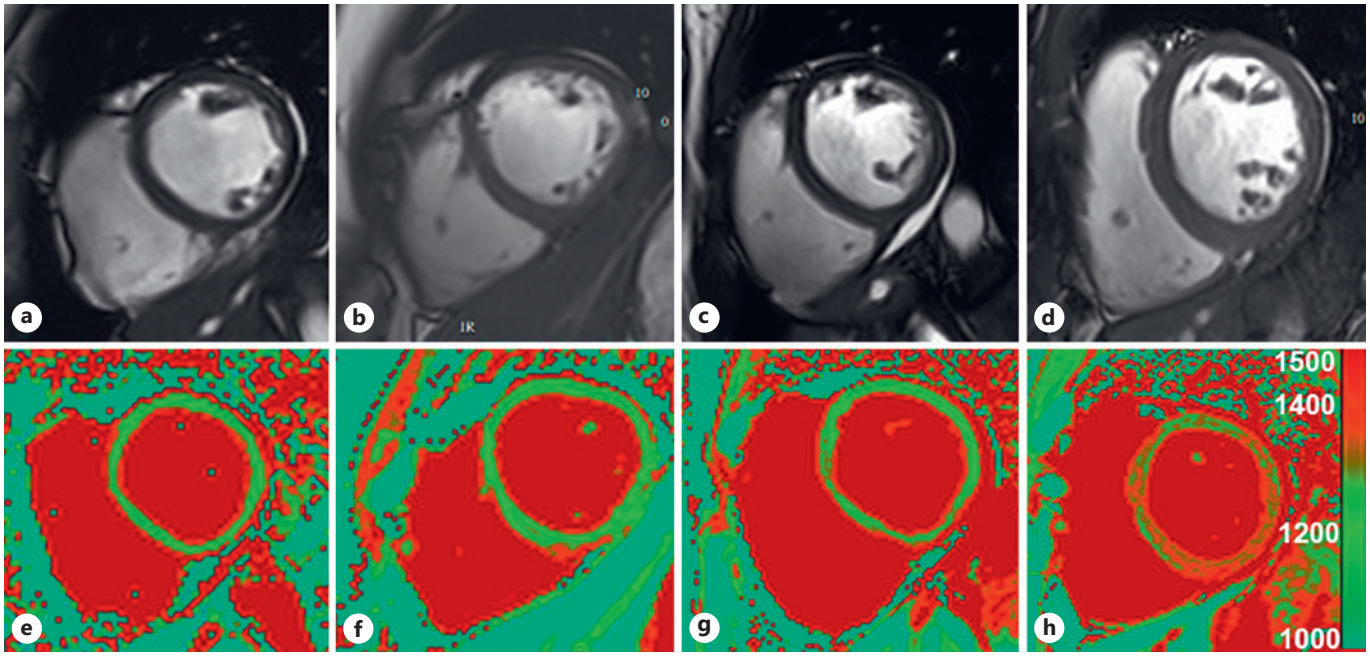

Fig. 1. Representative examples in HC and CKD groups. **a**–**d** are end-diastole cine images of short-axis view. **e**–**g** are native T1 map images. Normal myocardium appears green, with red representing elevated T1 values. **a**, **e** were acquired in a 45-year-old woman from HC group (LVMi was 32.17 g/m^2, RVMi was 9.46 g/m^2, native T1 value was 1,231.58 ms). **b**, **f** were acquired in a 50-year-old woman from CKD 1 group (LVMi was 37.75 g/m^2, RVMi was 9.68 g/m^2, native T1 value was 1,230.59 ms). **c**, **g** were acquired in a 43-year-old woman from CKD 2-3 group (LVMi was 53.03 g/m^2, RVMi was 14.87 g/m^2, native T1 value was 1,270.67 ms). **d**, **h** were acquired in a 41-year-old man from CKD 4-5 group (LVMi was 74.21 g/m^2, RVMi was 17.91 g/m^2, native T1 value was 1,364.83 ms).

LVEF in CKD 4-5 group was reduced. In addition, in terms of changes in properties of myocardial tissue, LV native T1 value elevated significantly in CKD 4-5 group compared with the other three groups (p = 0.004). Representative examples in HC and CKD groups are shown in Figure 1.

Intraobserver Reproducibility and Validation of CMR Measurements

Interobserver reproducibility was excellent for LV function (ICC = 0.992, p < 0.001), RV function (ICC = 0.982, p < 0.001), LV strain (ICC = 0.999, p < 0.001), RV strain (ICC = 0.940, p < 0.001), and native T1 value (ICC = 0.944, p < 0.001).

Correlations between CMR and Clinical Variables

All variables showing p value <0.1 at univariate analysis were included in the multivariate analysis (Table 3). Elevated LVESVi (β = 0.356, p = 0.016) and RVESVi (β = 0.488, p = 0.001) were independently associated with RVMi. Increased SBP (β = 0.309, p = 0.004), LVESVi (β = 0.633, p < 0.001), and uric acid (β = 0.261, p = 0.013) were independently associated with LVMi. Meanwhile, blood phosphorus (β = 0.519, p = 0.001) was independently associated with native T1 value.

Discussion

In our study, the comparison of right and LV CMR parameters across the CKD stage before dialysis yielded new insights. First, RV remolding has occurred in pre-dialysis CKD patients although RV function was still maintained. Second, RVMi and LVMi were the earliest changed CMR parameters during the development and progression of CKD, which occurred when the eGFR began to drop. The native T1 value was elevated when eGFR dropped below 30 mL/min/1.73 m^2. Third, RVMi and LVMi were independently correlated with ventricular volume indexes, while T1 value was independently associated with blood phosphorus.

RV dysfunction, defined as evidence of abnormal RV structure or function, is associated with poor clinical outcomes [21]. But the change of RV structure and function across stages of CKD before dialysis was not well studied by

Table 3. Independent correlates for RVMi, LVMi, and native T1 value in CKD patients

Variables	Univariable analysis		Multivariable analysis	
	β-coefficient	*p* value	β-coefficient	*p* value
RVMi				
Male gender	0.41	0.003	NS	0.185
LVESVi	0.72	<0.001	0.36	0.016
LVMi	0.51	<0.001	NS	0.420
RVESVi	0.75	<0.001	0.49	0.001
LVGRS	−0.43	0.002	NS	0.634
RVGCS	0.38	0.008	NS	0.762
LVMi				
Male gender	0.29	0.041	NS	0.334
SBP	0.54	<0.001	0.31	0.004
eGFR	0.54	<0.001	NS	0.681
Blood hemoglobin	0.37	0.008	NS	0.216
Blood phosphorus	0.60	<0.001	NS	0.250
Uric acid	0.27	0.06	0.26	0.013
LVESVi	0.74	<0.001	0.63	<0.001
RVEDVi	0.61	<0.001	NS	0.917
RVMi	0.51	<0.001	NS	0.684
LVGCS	0.51	<0.001	NS	0.170
Beta-blocker	0.29	0.046	NS	0.054
Native T1 value				
Duration of CKD	0.46	0.001	NS	0.070
Male gender	0.39	0.004	NS	0.245
HR	0.24	0.096	NS	0.412
SBP	0.32	0.027	NS	0.932
Blood phosphorus	0.42	0.006	0.52	0.001
eGFR	−0.42	0.002	NS	0.555
Blood hemoglobin	−0.30	0.031	NS	0.553
LVSVi	0.31	0.026	NS	0.183
ACEi/ARB	0.32	0.028	NS	0.133
Beta-blocker	0.48	<0.001	NS	0.099

RVMi, right ventricular mass index; LVMi, left ventricular mass index; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; LVESVi, left ventricular end-systolic volume index; LVSVi, left ventricular stroke volume index; LVGRS, left ventricular global radial strain; LVGCS, left ventricular global circumferential strain; RVESVi, right ventricular end-systolic volume index; RVEDVi, right ventricular end-diastolic volume index; RVGCS, right ventricular global circumferential strain; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NS, no significance; HR, heart rate.

CMR. In our study, there was an increasing trend in RVMi although no significant difference was observed between CKD 1 group and HC group, while RV function was maintained before dialysis. The increase of RVMi has shown prognostic information in patients with idiopathic pulmonary arterial hypertension and functional tricuspid regurgitation [22, 23]. However, its prognostic value in CKD patients remains unclear and requires further study. RV functional indexes, including RVEF and strain parameters, were not deteriorative in CKD groups when compared with HC group in our study, although in patients with eGFR <30 mL/min/1.73 m^2, RVEDVi and RVSVi were increased, representing an increase in blood volume. Nevertheless, noticeably impaired RV function has been shown in ESRD patients [9, 24] who had little discrepancy in eGFR compared with our patients in CKD 4-5 group. This distinction of RV function may be mostly contributed to dialysis. Studies have shown the patients on regular dialysis therapy may develop pulmonary hypertension and RV impairment, which were more pronounced in patients undergoing hemodialysis compared with patients receiving peritoneal dialysis [9]. Arteriovenous fistula in hemodialysis patients causes a left-to-right shunt and leads to chronic volume overload, resulting in RV remolding and functional decrease. Another possible reason is that we included patients with preserved LVEF and excluded patients with renal

etiologies that may cause cardiac structure and function abnormality.

Our study investigated the change pattern of biventricular CMR parameters. RVMi and LVMi were the earliest changed CMR parameter in the development of CKD, followed by LV strain indexes and native T1 value. Although the prognostic value of RVMi remains unclear, LVMi has been verified to be associated with adverse outcomes in pre-dialysis patients [10], indicating that LV hypertrophy may be one of the reasons for the increased risk of CVD in patients with mild-to-moderate CKD. When eGFR dropped to below 30 mL/min/1.73 m^2, LVGRS and LVGCS began to decrease, implying subclinical LV dysfunction with preserved LVEF. Another CMR parameter that changed significantly when the eGFR dropped to below 30 mL/min/1.73 m^2 was LV native T1 value. As one of the noninvasive methods to assess myocardial fibrosis, native T1 value derived by T1 mapping has been more widely applied in CKD patients compared with extracellular volume and late gadolinium enhancement due to the limitations of gadolinium administration. The increased native T1 value may indicate the presence of myocardial fibrosis in CKD 4-5 group patients. However, myocardial fibrosis and edema may represent the pathological background of elevated native T1 value. An increased native T2 value has also been revealed in patients with eGFR <30 mL/min/1.73 m^2 in recent studies [16, 17], implying the presence of myocardial edema. Thus, the contribution of elevated native T1 value caused by myocardial fibrosis is unclear.

We also explored the independent correlations between biventricular mass and ventricular volume indexes, which suggest that fluid retention may be one of the causes of cardiac remodeling in pre-dialysis patients. Reasonable fluid volume overload control may slow down the progression of RVMi and LVMi and may reduce related CVD risk. Besides, the increase of SBP may be also one reason of LV remodeling because of the independent association between LVMi and SBP. Higher serum phosphorus has been found to be associated with increased adverse events and cardiovascular-related mortality in patients with CKD [25, 26]. Serum phosphorus has been verified to be independently associated with LVMi and the prevalence of eccentric LVH in patients with CKD [27]. However, serum phosphorus was independently correlated with native T1 value, indicating the increase of serum phosphorus may be related to myocardial edema and/or myocardial fibrosis. The exact mechanisms responsible for those results remain unclear and further research is required.

Limitations

Our study had several limitations. First, this study had inherent limitations associated with retrospective data collection. Many clinical measures, such as N-terminal-brain natriuretic peptide, could not be analyzed because of their lack in more than 20% patients. Second, there was a small number of patients included, especially in each subgroup of CKD patients. This small sample size is mainly because patients were recruited with strict inclusion and exclusion criteria to minimize the effect of confounding factors on cardiac structure and function. Third, only a few patients underwent T2 mapping and gadolinium-based contrast-enhanced CMR; thus, relevant data were not analyzed in our study. A prospective study with large sample size is needed in the future.

Conclusions

In CKD patients before dialysis, left and right ventricular remolding has occurred. RVMi and LVMi were the first changed CMR indexes in the development of CKD when eGFR began to drop. Because fluid volume overload was the independent risk factor for RVMi and LVMi increase, reasonable controlling fluid volume overload may slow down the progression of biventricular remolding and may reduce related CVD risk.

Statement of Ethics

This study was approved by the Institutional Review Board of Jinlin hospital (approval number: 2015NZGKJ-085) and written informed consent was waived from all the participants.

Conflict of Interest Statement

The other authors have no conflicts of interest to declare.

Funding Sources

This work was financed by Grant-in-Aid for Scientific Research from the National Natural Science Foundation for the Youth of China (No. 81501448).

Author Contributions

Long Jiang Zhang, Song Luo, and Li Qi contributed to the conception of the study; Li Qi, Beibei Zhi, Lingyan Zhang, and

Jun Zhang contributed to data acquisition; Li Qi and Beibei Zhi performed the image analysis; Li Qi wrote this manuscript; and Long Jiang Zhang reviewed and edited this manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Jankowski J, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular disease in chronic kidney disease: pathophysiological insights and therapeutic options. Circulation. 2021 Mar;143(11):1157–72.
2 United States Renal Data System [Internet]. Basel: 2020 annual data report: chronic kidney disease: 4: cardiovascular disease in patients with CKD. Available from: https://usrds-adr.niddk.nih.gov/2020/chronic-kidney-disease/4-cardiovascular-disease-in-patients-with-ckd.
3 Menon V, Gul A, Sarnak MJ. Cardiovascular risk factors in chronic kidney disease. Kidney Int. 2005 Oct;68(4):1413–8.
4 Rutherford E, Mark PB. What happens to the heart in chronic kidney disease? J R Coll Physicians Edinb. 2017 Mar;47(1):76–82.
5 Lundorff IJ, Sengeløv M, Pedersen S, Modin D, Bruun NE, Fritz-Hansen T, et al. Prognostic value of right ventricular echocardiographic measures in patients with heart failure with reduced ejection fraction. J Clin Ultrasound. 2021 Nov;49(9):903–13.
6 Dong Y, Pan Z, Wang D, Lv J, Fang J, Xu R, et al. Prognostic value of cardiac magnetic resonance-derived right ventricular remodeling parameters in pulmonary hypertension: a systematic review and meta-analysis. Circ Cardiovasc Imaging. 2020 Jul;13(7):e010568.
7 Ancona F, Melillo F, Calvo F, Attalla El Halabieh N, Stella S, Capogrosso C, et al. Right ventricular systolic function in severe tricuspid regurgitation: prognostic relevance of longitudinal strain. Eur Heart J Cardiovasc Imaging. 2021 Jul;22(8):868–75.
8 Patel AR, Kramer CM. Role of cardiac magnetic resonance in the diagnosis and prognosis of nonischemic cardiomyopathy. JACC Cardiovasc Imaging. 2017 Oct;10(10 Pt A):1180–93.
9 Paneni F, Gregori M, Ciavarella GM, Sciarretta S, De Biase L, Marino L, et al. Right ventricular dysfunction in patients with end-stage renal disease. Am J Nephrol. 2010;32(5):432–8.
10 Lee SW, Min HK, Chae DW, Oh KH, Ahn C, Chung W, et al. Indexation of left ventricular mass to predict adverse clinical outcomes in pre-dialysis patients with chronic kidney disease: Korean cohort study of the outcome in patients with chronic kidney disease. PLoS One. 2020 May;15(5):e0233310.
11 Graham-Brown MPM, Patel AS, Stensel DJ, March DS, Marsh AM, McAdam J, et al. Imaging of myocardial fibrosis in patients with end-stage renal disease: current limitations and future possibilities. Biomed Res Int. 2017;2017:5453606.
12 Tanasa A, Burlacu A, Popa IV, Covic A. Right ventricular functionality following hemodialysis initiation in end-stage kidney disease-a single-center, prospective, cohort study. Medicina. 2021 Jul;57(7):704.
13 Hunold P, Vogt FM, Heemann UW, Zimmermann U, Barkhausen J. Myocardial mass and volume measurement of hypertrophic left ventricles by MRI–study in dialysis patients examined before and after dialysis. J Cardiovasc Magn Reson. 2003;5(4):553–61.
14 Sugeng L, Mor-Avi V, Weinert L, Niel J, Ebner C, Steringer-Mascherbauer R, et al. Multimodality comparison of quantitative volumetric analysis of the right ventricle. JACC Cardiovasc Imaging. 2010 Jan;3(1):10–8.
15 Kis E, Ablonczy L, Reusz GS. Cardiac magnetic resonance imaging of the myocardium in chronic kidney disease. Kidney Blood Press Res. 2018;43(1):134–42.
16 Arcari L, Engel J, Freiwald T, Zhou H, Zainal H, Gawor M, et al. Cardiac biomarkers in chronic kidney disease are independently associated with myocardial edema and diffuse fibrosis by cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2021 Jun 7;23(1):71.
17 Hayer MK, Price AM, Liu B, Baig S, Ferro CJ, Townend JN, et al. Diffuse myocardial interstitial fibrosis and dysfunction in early chronic kidney disease. Am J Cardiol. 2018 Mar;121(5):656–60.
18 Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int. 2011 Jul;80(1):17–28.
19 Stevens PE, Levin A; Kidney Disease Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med. 2013 Jun;158(11):825–30.
20 Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med. 2016 Jun;15(2):155–63.
21 Konstam MA, Kiernan MS, Bernstein D, Bozkurt B, Jacob M, Kapur NK, et al. Evaluation and management of right-sided heart failure: a scientific statement from the American Heart Association. Circulation. 2018 May;137(20):e578–622.
22 Grapsa J, Tan TC, Nunes MCP, O'Regan DP, Durighel G, Howard LSGE, et al. Prognostic impact of right ventricular mass change in patients with idiopathic pulmonary arterial hypertension. Int J Cardiol. 2020 Apr;304:172–4.
23 Ahn Y, Koo HJ, Kang JW, Choi WJ, Kim DH, Song JM, et al. Prognostic implication of right ventricle parameters measured on preoperative cardiac MRI in patients with functional tricuspid regurgitation. Korean J Radiol. 2021 Aug;22(8):1253–65.
24 Peng W, Li Z, Xu H, Xia C, Guo Y, Zhang J, et al. Assessment of right ventricular dysfunction in end-stage renal disease patients on maintenance haemodialysis by cardiac magnetic resonance imaging. Eur J Radiol. 2018 May;102:89–94.
25 Weinman EJ, Light PD, Suki WN. Gastrointestinal phosphate handling in CKD and its association with cardiovascular disease. Am J Kidney Dis. 2013 Nov;62(5):1006–11.
26 Dominguez JR, Kestenbaum B, Chonchol M, Block G, Laughlin GA, Lewis CE, et al. Relationships between serum and urine phosphorus with all-cause and cardiovascular mortality: the osteoporotic fractures in men (MrOS) study. Am J Kidney Dis. 2013 Apr;61(4):555–63.
27 Zou J, Yu Y, Wu P, Lin FJ, Yao Y, Xie Y, et al. Serum phosphorus is related to left ventricular remodeling independent of renal function in hospitalized patients with chronic kidney disease. Int J Cardiol. 2016 Oct;221:134–40.