Association between Reduced estimated Glomerular Filtration Rate and Cardiac Structure and Function in Patients with Essential Hypertension

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Abstract

Objectives To investigate the relationship between small reductions in estimated glomerular filtration rate (eGFR) and cardiac structure and function in patients with essential hypertension. **Methods** The study group included 565 patients with essential hypertensive. eGFR was calculated by EPI equation and cardiac structure and function were assessed using echocardiography. The participants were divided into three groups: eGFR ≥ 90 mL/min/1.73 m², 60-89 mL/min/1.73 m², and 30-59 mL/min/1.73 m². Pearson correlation analysis and multiple stepwise linear regression analysis were performed to evaluate associations between eGFR and echocardiogram parameters. **Results** Compared with patients with eGFR ≥ 90 mL/min/1.73 m², those with eGFR 60-89 mL/min/1.73 m² and 30-59 mL/min/1.73 m² had higher left ventricular end-diastolic diameter (LVEDD) ($p=0.019$), mitral valve E wave ($p=0.004$), left atrial diameter (LAD) ($p=0.001$), right atrial diameter (RAD) ($p=0.001$), right ventricular diameter (RVD) ($p=0.001$) and lower left ventricular ejection fraction (LVEF) ($p=0.01$). After further adjustment for traditional cardiovascular risk factors including systolic and diastolic blood pressure, BMI, diabetes, dyslipidemia and smoking, eGFR was still associated with LVEF ($p<0.001$), LAD ($p<0.001$) and RAD ($p=0.003$). **Conclusion** Among patients with essential hypertension, even mildly reduced renal function is independently associated with greater cardiac remodeling, indicated by left atrial and right atrial enlargement, and worse left ventricular systolic function.

Introduction

Hypertension is one of the major risk factors for the heart failure progression¹ and is associated with cardiac structure remodeling, impaired myocardial function, and renal dysfunction². Previous studies have shown that chronic kidney disease (CKD) carries a high risk for all-cause and cardiovascular mortality³⁻⁵ across the spectrum of cardiovascular disease⁶, including hypertension. On the other hand, the high prevalence of hypertension in CKD patients may also contribute to the development and acceleration of cardiac disease.

Despite the high incidence of cardiac and renal diseases in hypertension patients, the mechanisms relating them are still not very clear. Elucidating these mechanisms is crucial for designing and implementing preventive strategies to reduce vascular morbidity in this population. Furthermore, the relationship between small reductions in estimated glomerular filtration rate (eGFR) and cardiac structural and functional abnormalities have not been extensively investigated.

Based on previous data, we hypothesized that the interplay between impaired kidney function and cardiac structure begins at the early stage of CKD with eGFR >60 mL/min/1.73 m². To explore this hypothesis, we investigated the cross-sectional associations between eGFR, echocardiogram parameters and cardiac function in patients with essential hypertension.

Methods

Subjects From July 2017 to November 2019, 594 patients with essential hypertension from the cardiovascular department of Beijing Tiantan Hospital were recruited. The inclusion criterion was a diagnosis of essential hypertension according to 2005 Chinese guidelines for the prevention and treatment of patients with hypertension [14]. Exclusion criteria included eGFR ≤ 30 mL/min/1.73m² or on dialysis therapy, secondary hypertension, malignancy and mental disorders. Of the 594 participants, 29 patients were excluded and 565 patients were included in the final analysis. Prior informed consent was obtained from all patients in the study. This study was approved by the Ethics Committee of Beijing Tiantan Hospital.

Clinical and biochemical evaluation

Data on comorbid conditions were collected at time of enrollment based on the medical history. In addition, information regarding patient medications, including angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), β -blockers, calcium channel blockers and diuretics, during the study period was obtained from medical records. The body mass index (BMI) was calculated as the ratio of the weight in kilograms divided by square of height in meters (kg/m²).

Venous blood samples were drawn in the morning after an overnight fast and stored at -70°C. All laboratory indicators were analyzed with standard procedures at the department of clinical chemistry at Beijing Tiantan Hospital.

eGFR was calculated by the CKD-EPI China equation with adjusted coefficient of 1.1 for the Chinese population⁷: $eGFR_{CKD-EPI(CN)} = 141 \times \min(SCr/k, 1)^\alpha \times \max(SCr/k, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ (if female) $\times 1.1$, where SCr is serum creatinine, k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min is the minimum of SCr/k or 1, and max indicates the maximum of SCr/k or 1. Patients were divided into the following groups: eGFR ≥ 90 mL/min/1.73 m² (normal renal function), 60 to 89 mL/min/1.73 m² (mild CKD), and 30-59 mL/min/1.73 m² (moderate CKD) based on the NKF-KDOQI (National Kidney Foundation Kidney Disease Outcomes Quality Initiative) guidelines⁸.

Echocardiography

The cardiac function and structure of the study participants were evaluated by 2D transthoracic echocardiography with a 1.4-4.6MHz, M5Sc-D probe (GE Vivid E95, USA). The echocardiographic examination was performed by two experienced and registered cardiologists. Left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), inter-ventricular septum diastolic thickness (IVST), left ventricular posterior wall thickness (LVPW), left atrial diameter (LAD), aorta sinus diameter (ASD), main pulmonary artery diameter (MPAD), right atrial diameter (RAD), right ventricular diameter (RVD) were measured according to the guidelines of the American Society of Echocardiography⁹. Left ventricular systolic function can be estimated by a conventional method. LVEF was obtained from apical 4-chamber and/or two-chamber view by using the biplane Simpson's method from LV end-diastolic and end-systolic volume. LVEF calculation formula: $LVEF = (LVEDV - LVESV) / LVEDV \times 100\%$. LV diastolic function, including the peak velocities of early (E) and late (A) transmitral flow velocities, the ratio of early to late peak velocities (E/A) were measured. The mitral flow velocity was assessed by pulsed wave Doppler study from the apical 4-chamber view by positioning the sample volume at the tip of the mitral leaflets.

Statistical Analysis

Continuous data are presented as mean and standard deviation or median and inter-quartile range and categorical variables as counts and percentage. Clinical characteristics and cardiovascular structure and function were compared between different groups of hypertension patients according to the category of renal function. Comparisons between eGFR category groups were conducted using the χ^2 test for categorical variables, and one-way analysis of variance or non-parametric trend tests for continuous variables. Univariate associations between the eGFR and echocardiogram parameters were assessed by the Pearson correlation coefficients. Multiple stepwise linear regression analysis was performed to assess the independent associations between eGFR and echocardiogram parameters (as the dependent variable) with adjustment for the potential confounding factors including age, sex, systolic and diastolic blood pressure, BMI, diabetes, dyslipidemia

and smoking. P-values < 0.05 were considered statistically significant.

Results

Patient Characteristics

The clinical and laboratory characteristics of the study participants according to renal function categories are summarized in Table 1. Compared with patients with eGFR ≥ 90 mL/min/1.73 m², patients with the lower eGFR were older and had a higher prevalence of cerebrovascular disease and atrial fibrillation. They also had, on average, lower diastolic blood pressure, higher BUN and uric acid. There were no significant differences in gender, BMI, history of diabetes, smoking, lipid metabolism disorder, systolic blood pressure, heart rate and lipid level in these three eGFR category groups ($P > 0.05$). Patients with lower eGFR had higher diuretic therapy use compared with those with more preserved renal function.

Echocardiographic Measurements of Study Participants according to Renal Function

Measurements of cardiac structure and function according to the renal function are listed in Table 2. The patients with eGFR 60-89 mL/min/1.73 m² and 30-59 mL/min/1.73 m² had lower LVEF compared with those with eGFR ≥ 90 mL/min/1.73 m², but the difference did not reach statistical significance (63.22 ± 6.91 , 61.29 ± 10.96 vs 64.66 ± 6.25 , $p = 0.10$). However, LVEDD ($p = 0.019$), mitral valve E wave ($p = 0.004$) and LAD ($p = 0.001$) significantly increased as eGFR declined. In the same trend, parameters reflecting the right cardiac structure including RA ($p = 0.001$) and RVD ($p = 0.001$) were higher in patients with eGFR 60-89 mL/min/1.73 m² and 30-59 mL/min/1.73 m² compared with those with eGFR ≥ 90 mL/min/1.73 m².

Associations between eGFR and Different Echocardiographic Variables

After adjustment for age and sex, eGFR, as a continuous variable, remained significantly associated with LVEF ($p < 0.001$) (Table 3). Concordant with this systolic function, eGFR was also associated with remodeling impairment as reflected by both LAD ($p < 0.001$) and RA ($p = 0.003$). After further adjustment for other traditional cardiovascular risk factors including systolic and diastolic blood pressure, BMI, diabetes, LDL-cholesterol and smoking, there remained a significant relationship between eGFR and the above echocardiographic parameters.

Discussion

Our main findings from this cross-sectional study demonstrate that, in patients with essential hypertension, echocardiographic parameters changed in a graded manner as eGFR declined, even in mild renal dysfunction (eGFR 60-89 mL/min). Second, we also find that there was an independent association between eGFR and echocardiographic markers of cardiac structure and function, including left atrial and right atrial enlargement and LVEF.

In the present study, we found that LVEF, LVEDD, peak velocity of blood flow through the mitral valve in early E diastole (mitral valve E wave) and LAD increased as eGFR declined. Emerging data have shown an association between renal dysfunction and systolic and diastolic left ventricular function in CKD. Left ventricular hypertrophy (LVH) is one of the most common cardiac structure abnormalities in hypertension, due to heavy left ventricular load. Recent studies¹⁰⁻¹² demonstrated that LVH is highly prevalent in patients with CKD; in this population, LVH is often characterized by the simultaneous increase of wall thicknesses and diameters. In accordance with our study, previous studies¹³ conducted in CKD patients demonstrated that LVEDD, LA, RWT, and LVMI were distinctly higher in poorly controlled hypertensive patients. Similarly, in two community-based cohorts¹⁴ of elderly, higher eGFR was significantly associated with higher LVEF after adjustment for cardiovascular risk factors. Our results demonstrated that in even mild CKD (eGFR 60-89 mL/min/1.73 m²) patients with hypertension, left cardiac involvement starts early, which may be a precursor of premature cardiac morbidity.

Apart from left ventricular structure and function, we also observed increases in linear measures of dimensions of right atrial and right ventricular chamber size as renal function declined, and there was a significant

association between right atrial enlargement and eGFR after adjustment for multiple risk factors. Contemporary clinical and hemodynamic studies have shown that high right atrial pressure, signs of venous congestion, was linked to renal dysfunction in acute¹⁵ and chronic heart failure^{16, 17}, pulmonary hypertension¹⁸, and patients undergoing right heart catheterization for various clinical indications¹⁹. In addition, right ventricular dysfunction prospectively predicts survival in CKD patients with chronic heart failure^{20, 21}. These data suggest right-sided cardiac dysfunction to be one of the possible mechanistic links between heart failure and CKD.

High blood pressure is a major promoter of the decline in GFR²², and vice versa, the development of CKD is per se a cause of secondary hypertension and can worsen a preexisting hypertension^{23, 24}. The incidence of cardiovascular disease progressively increases as GFR deteriorates, reaching dramatically high levels in patients on renal replacement therapy. This is mainly due to the multifactorial pathogenesis of cardiac structure and function abnormalities in renal patients where both hemodynamic and non-hemodynamic stimuli synergistically act²⁵. The underlying mechanisms include hypervolemia, anemia, increased neurohormone activation, secondary hyperparathyroidism (SHPT) and mineral metabolism disorders²⁵.

There are several limitations in the present investigation. First, due to the cross-sectional nature of the data, we are unable to draw conclusions regarding changes over time in the variables studied. Second, the proportion of patients with mild-to-moderate CKD was relatively small. However, eGFR showed independent correlation with cardiac structure and function after adjusting for multiple risk factors. In the future, large clinical trials are needed to confirm the relation between renal insufficiency and cardiac structure and dysfunction.

In conclusion, our survey suggests that among patients with essential hypertension, even mildly reduced renal function is independently associated with greater cardiac remodeling, indicated by left atrial and right atrial enlargement, and worse left ventricular systolic function.

Compliance with ethical standards All procedures performed in this study 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. For this type of study, formal consent is not required.

Competing interests The authors declare that they have no competing interests.

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Table 1 Clinical and Laboratory Characteristics of Study Participants according to Renal Function Group

	All patients	eGFR [?]90 mL/min/1.73m ²	eGFR 60-89 mL/min/1.73m ²	eGFR 30-59 mL/min/1.73m ²	P value
number	565	445	91	29	
Age,years	63.70±10.79	62.47±9.46	68.96±13.27	73.05±9.21	¡0.001
Female (%)	224(40.1)	170(38.6)	38(42.2)	16(55.2)	0.17
BMI, kg/m²	26.49±11.45	26.45±3.50	26.90±4.51	26.87±7.07	0.06
Smoker,%	278	225	41	12	0.476
Medical history, %					
Diabetes	234(41.4)	179(40.2)	41(45.1)	14(48.3)	0.46
Cerebrovascular disease	123(21.8)	86(19.3)	27(29.7)	10(34.5)	0.02
Atrial fibrillation	59(10.4)	36(8.1)	14(15.4)	9(31.0)	<0.001
Dyslipidemia	395(69.9)	304(68.3)	72(79.1)	19(65.5)	0.115
SBP,mmHg	132.45±19.37	131.90±18.81	133.21±19.97	132.55±18.48	0.72
DBP,mmHg	78.37±12.66	78.96±12.66	75.88±12.30	74.07±10.07	0.02
Heart rate	73.00±11.62	72.38±11.38	71.49±12.08	74.48±11.67	0.54
Laboratory parameters					
LDL-cholesterol(mmol/L)	2.28±0.80	2.26 ±0.74	2.06±0.75	2.09±0.88	0.360
HDL-cholesterol(mmol/L)	1.07±0.28	1.06±0.28	1.07±0.29	1.07±0.30	0.986
TC(mmol/L)	3.86±0.92	3.89±0.89	3.72±0.98	3.79±1.11	0.283
TG(mmol/L)	1.67±1.15	1.71±1.15	1.49±1.21	1.47±0.77	0.169
Creatinine(umol/L)	109.02±21.78	62.36±12.89	84.84±20.93	121.48±33.88	<0.001
BUN(mmol/L)	6.17±3.38	5.68±3.25	7.05±1.72	10.92±4.96	¡0.001
UA(umol/L)	360.36±89.69	349.74±83.72	388.01±98.65	436.17±96.77	¡0.001
Medications, %					
ACEI/ARB	385(68.1)	304(68.3)	62(68.1)	19(65.5)	0.965
Beta-blocker	375(66.4)	290(65.2)	61(67.0)	24(82.8)	0.101
Calcium channel blocker	342(60.5)	275(61.8)	47(51.7)	20(69.0)	0.177
Diuretic	123(21.8)	78(7.5)	31(34.1)	14(48.3)	¡0.001
Alpha-blocker	14(2.5)	11(2.5)	2(2.2)	1(3.5)	0.927

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TC, total cholesterol; TG, triglycerides; BUN, urea nitrogen; UA, uric acid; ACEI, angiotensin

converting enzyme inhibitors; ARB, angiotensin II receptor blockers

Table 2 Echocardiographic Parameters of Study Participants according to Renal Function

	All patients	eGFR [?]90 mL/min/1.73m ²	eGFR 60-89 mL/min/1.73m ²	eGFR 30-59 mL/min/1.73m ²	P value
number	565	445	91	29	
LVEF, (%)	63.94±7.10	64.66±6.25	63.22±6.91	61.29±10.96	0.010
LVEDD, (mm)	45.43±4.49	45.21±3.95	45.91±4.78	46.52±8.60	0.019
IVST, (mm)	10.12±1.45	10.08±1.36	10.39±1.69	10.10±1.92	0.149
LVPW(mm)	9.69±1.10	9.65±1.06	9.81±1.18	10.00±1.58	0.185
Mitral valve E wave,(cm/s)	73.35±21.26	71.02±18.01	71.44±20.78	77.10±27.44	0.004
Mitral valve A wave,(cm/s)	84.76±20.89	83.56±20.46	86.78±21.30	94.24±21.30	0.119
E/A ratio	0.88±0.32	0.89±0.32	0.86±0.34	0.88±0.40	0.63
LAD, (mm)	34.76±4.67	33.90±3.75	35.31±4.28	35.52±6.14	0.001
ASD, (mm)	31.22±3.25	31.17±3.30	31.17±2.74	31.76±3.77	0.001
MPAD, (mm)	21.19±2.39	21.06±2.36	21.32±2.23	21.81±2.79	0.937
RAD, (mm)	43.50±5.30	42.59±4.01	43.70±5.16	43.90±5.99	0.001
RVD, (mm)	21.14±1.98	21.05±1.90	21.22±2.09	21.19±2.77	0.002

Abbreviations: LVEF ,Left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; IVST, inter-ventricular septum diastolic thickness;LVPW ,left ventricular posterior wall thickness; LAD,left atrial diameter;ASD aorta sinus diameter;MPAD,Main Pulmonary artery diameter;RAD,Right atrial diameter; RVD,Right ventricular diameter

Table 3 Associations between estimated Glomerular Filtration Rate and Different Echocardiographic Parameters

	Unadjusted	Unadjusted	Adjusted Model 1	Adjusted Model 1	Adjusted Model 2	Adjusted Model 2
	B- 95%CI	P	B- 95%CI	P	B- 95%CI	P
LVEF	0.179	0.001	0.133	0.001	0.112	0.001
LVEDD	-0.077	0.067	0.087	0.017	-0.076	0.063
Mitral valve E wave	-0.090	0.032	-0.089	0.015	-0.089	0.024
LAD	-0.211	0.001	-0.141	0.001	-0.151	0.001
ASD	-0.057	0.175	-0.082	0.025	-0.081	0.066
RAD	-0.196	0.001	-0.112	0.003	-0.112	0.005
RVD	-0.068	0.108	-0.064	0.086	-0.063	0.120

Abbreviations: LVEF ,Left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; IVST, inter-ventricular septum diastolic thickness;LVPW ,left ventricular posterior wall thickness; LAD,left

atrial diameter; ASD aorta sinus diameter; MPAD, Main Pulmonary artery diameter; RAD, Right atrial diameter; RVD, Right ventricular diameter

Model 1: adjusted age, sex.

Model 2: adjusted age, sex, systolic and diastolic blood pressure, BMI, diabetes, dyslipidemia and smoking.