Effect of Renal Dysfunction on Risk of Sudden Cardiac Death in Patients With Hypertrophic Cardiomyopathy

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Renal dysfunction is a known risk of sudden cardiac death in patients with ischemic heart disease. However, the association between renal dysfunction and sudden death in hypertrophic cardiomyopathy (HC) patients remains unknown. This study investigated the significance of an impaired renal function for the sudden death risk in a cohort of patients with HC. We included 450 patients with HC (mean age 52.9 years, 65.1% men). The estimated glomerular filtration rate (eGFR) was evaluated at the time of the initial evaluation. Renal dysfunction was defined as an eGFR <60 ml/min/1.73 m^2. Renal dysfunction was found in 171 patients (38.0%) at the time of enrollment. Over a median (IQR) follow-up period of 8.8 (5.0 to 12.5) years, 56 patients (12.4%) experienced the combined end point of sudden death or potentially lethal arrhythmic events, including 20 with sudden death (4.4%), 11 resuscitated after a cardiac arrest, and 25 with appropriate implantable defibrillator shocks. Patients with renal dysfunction were at a significantly higher risk of sudden death (Log-rank p = 0.034) and the combined end point (Log-rank p <0.001) than patients without renal dysfunction. After adjusting for the highly imbalanced baseline variables, the eGFR remained as an independent correlate of the combined end point (adjusted hazard ratio: 1.24 per 10 ml/min decline in the eGFR; 95% confidence interval 1.04 to 1.47; p = 0.013). In conclusion, an impaired renal function may be associated with an incremental risk of sudden death or potentially lethal arrhythmic events in patients with HC. **(Am J Cardiol 2021;144:131−136)**

Sudden cardiac death (SCD) is the most common devastating consequence in patients with hypertrophic cardiomyopathy (HC). Clinical interest has focused on identifying patients at higher risk of SCD and preventing unfavorable outcomes.[1−4] However, the identification of the individuals most likely to benefit from prophylactic treatment with implantable cardioverter defibrillators (ICD) still remains challenging. Chronic kidney disease (CKD) is a worldwide public health problem that affects every population, especially those with organic heart disease.[5] Numerous studies have reported that in patients with ischemic heart disease, an impaired renal function faces an increased risk of cardiovascular disease mortality, particularly from SCD.[6−9] Recently, HC itself has been proposed as a novel risk factor for the development of renal dysfunction.[10,11] The incidence of developing renal dysfunction is higher in HC patients than non-HC subjects in all age groups and in both sexes.[10] However, there have been no data regarding whether an impaired renal function increases the risk of sudden and unexpected cardiac death in the HC population. Therefore, in the present study, we sought to investigate the significance of renal dysfunction for the risk of sudden death in a relatively large longitudinal cohort of patients with HC.

Methods

The study population included 491 consecutive patients (≧18 years of age) clinically diagnosed with HC at Tokyo Women's Medical University Hospital, Tokyo, Japan, from January 1, 2003 to October 31, 2016. The initial evaluation was the first clinical assessment during which patients were echocardiographically diagnosed with HC at our institution, and the most recent evaluation was undergone in the outpatient clinic until December 31, 2017. HC was diagnosed on the basis of the echocardiographic evidence of a hypertrophied nondilated left ventricle (LV) and in the absence of any other cardiac or systemic disease capable of producing a similar degree of hypertrophy.[1,2] Other clinical parameters were recorded, including the New York Heart Association (NYHA) functional class, medication use, results of ambulatory electrocardiograms covering at least a 24-hour period, presence or absence of nonsustained ventricular tachycardia (minimum of 3 consecutive ventricular extrasystoles at a rate of ≧120 beats/min and lasting for <30 seconds), family history of SCD, and patient history of unexplained syncope. This study was conducted according to the principles of the Declaration of Helsinki, and the study protocol was approved by the ethics committee of our institution.

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See page 135 for disclosure information.

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Among 491 patients with HC, 41 were excluded from the present study for the following reasons: 7 who were dialysis dependent at the time of the initial evaluation, 24 who had no available blood samples for calculating the eGFR, and 10 who were lost during follow-up. After those exclusions, 450 patients remained eligible for the present study.

Each patient underwent an evaluation of their estimated glomerular filtration rate (eGFR) at the time of the initial evaluation. The eGFR was calculated using the modification of the diet in the renal disease formula.[12] The CKD stage was defined according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines.[13] In the present study, renal dysfunction was defined as an eGFR <60 ml/min/1.73 m^2.[13]

Each patient underwent transthoracic echocardiography using commercially available ultrasound equipment. The LV end-diastolic diameter was measured from 2-dimensional images and M-mode obtained from the parasternal long-axis views. The left atrial dimension measured from the parasternal long-axis view was defined as the anteroposterior linear diameter during end-systole. The maximum LV wall thickness was measured at the greatest thickness in any single segment. We calculated the ratio of the E peak velocity to the average e′ peak velocity (E/e′ ratio) using Tissue Doppler imaging at the septal side of the mitral annulus. Sites where a LV intracavitary obstruction existed were localized by color Doppler echocardiography and pulsed wave Doppler echocardiography. The definition of an LV outflow tract obstruction was demonstrated in previous studies.[1,2,4]

The 2 study end points in this study were as follows: (1) sudden death (unexpected death occurring in the absence of symptoms or within 1 hour of the onset of symptoms in patients with a relatively stable or uneventful course) and (2) the combination of sudden death, successful resuscitation after cardiac arrest (ventricular tachycardia or ventricular fibrillation with pulseless collapse) or appropriate ICD shocks. All events were identified and classified at the time of the occurrence by experienced cardiologists and electrophysiologists and also subsequently ascertained by the study investigators through reviewing the medical records.[1–4]

We retrospectively analyzed the clinical characteristics, eGFR at the time of the initial evaluation, and outcomes during the follow-up. The results are presented as the mean ± standard deviation and median (interquartile range [IQR]) or frequency (percentage). We used Student's *t* tests to compare the normally distributed continuous variables, and Mann-Whitney *U* tests to analyze the skewed continuous or ordinal variables between the groups. We compared the nominal variables using Chi-square tests or Fisher's exact tests (when an expected value was <5). The event-free curves were estimated using the Kaplan-Meier method, and differences between the curves were assessed by log-rank tests. Cox proportional hazards models were used to examine the association between the eGFR and combined endpoint of sudden death or potentially lethal arrhythmic events and verified by the proportionality assumptions of all models. Because of the small number of endpoints, we avoided including all potential confounders in 1 multivariable model and used 3 models to perform the multivariable analyses. Model 1 was adjusted for the age at the time of the evaluation and sex. Model 2 was adjusted for the age, sex, and established risk factors for SCD such as a family history of sudden death, maximum left ventricular wall thickness (analyzed as a continuous variable), nonsustained ventricular tachycardia, and unexplained syncope.[1] Model 3 was adjusted for the age, sex, and highly imbalanced baseline variables ($p < 0.05$). All tests were 2-sided, and statistical significance was set at a value of $p < 0.05$. All statistical analyses were performed using SPSS software version 23.0 (SPSS Inc, Chicago, Illinois).

Results

Over a median (IQR) follow-up period of 8.8 (5.0 to 12.5) years, a total of 56 patients (12.4%) experienced sudden death or potentially lethal arrhythmic events, including 20 (4.4%) with sudden death, 11 (2.4%) resuscitated after a cardiac arrest (4 with documented ventricular tachycardia with a pulseless collapse and 7 with documented ventricular fibrillation), and 25 (5.6%) with appropriate implantable defibrillator shocks. The median (IQR) time from the initial evaluation to sudden death was 5.0 (3.3 to 6.9) years and the median time from the initial evaluation to the combined endpoint was 5.1 (2.9 to 9.7) years.

The mean eGFR level among the HC cohort was 65.9 ± 18.4 ml/min/1.73 m^2. Box and whisker plots of the eGFR in patients without any events, with sudden death, and with the combined end point of sudden death or potentially lethal arrhythmic events are shown in Figure 1. The mean eGFR level in those with sudden death (58.1 ± 17.8 ml/min/1.73 m^2) and the combined end points of sudden death or potentially lethal arrhythmic events (58.2 ± 17.6 ml/min/1.73 m^2) were significantly lower than that in those without any events (67.3 ± 18.2 ml/min/1.73 m^2).

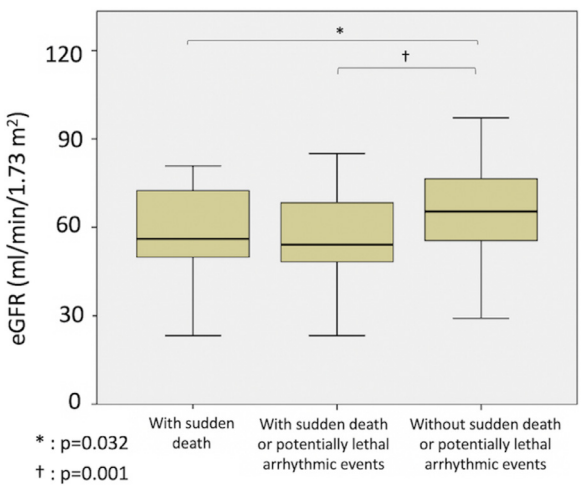

Figure 1. Box and whisker plots of the eGFR in the HC patients with sudden death, with the combined endpoint of sudden death or potentially lethal arrhythmic events and without any events. The line across each box represents the mean eGFR; the box represents the standard deviation; and the I bars represent the 95% confidence intervals. eGFR = estimated glomerular filtration rate; HC = hypertrophic cardiomyopathy.

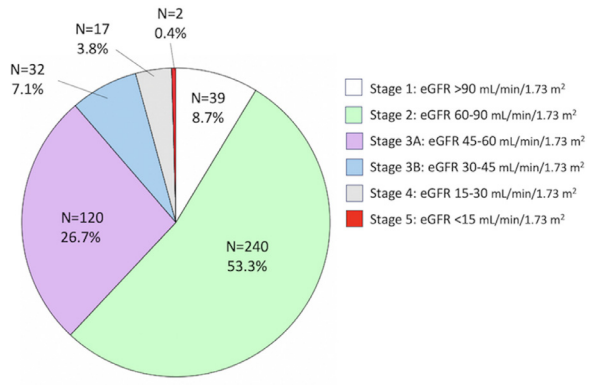

Figure 2. The prevalence of the CKD stage among 450 HC patients at the time of the initial evaluation. eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease; HC = hypertrophic cardiomyopathy.

Figure 2 shows the prevalence of the CKD stages among the 450 patients at the time of the initial evaluation. There was a total of 171 patients (38.0%) with renal dysfunction and 279 (62.0%) without renal dysfunction. The baseline clinical characteristics of the 2 groups are summarized in Table 1.

Over a median (IQR) follow-up period of 7.0 (3.7 to 10.7) years, 31 patients (18.1%) with renal dysfunction experienced sudden death or potentially lethal arrhythmic events, including 11 (6.4%) who experienced sudden death, 6 (3.5%) resuscitated after a cardiac arrest (4 with documented ventricular tachycardia with a pulseless collapse and 2 with documented ventricular fibrillation), and 14 (8.2%) with appropriate implantable defibrillator shocks. On the contrary, 25 patients (9.0%) without renal dysfunction experienced sudden death or potentially lethal arrhythmic events over a median (IQR) follow-up period of 10.2 (6.3 to 13.2) years, including 9 (3.2%) who experienced sudden death, 5 (1.8%) resuscitated after a cardiac arrest (5 with documented ventricular fibrillation), and 11 (3.9%) with appropriate implantable defibrillator shocks. The median time from the initial evaluation to the combine end point was 3.9 (2.4 to 7.1) years in those with renal dysfunction, whereas it was 8.0 (4.2 to 10.6) years in those without renal dysfunction. ICDs were finally implanted in 37 of the 171 patients (21.6%) with renal dysfunction and 42 of the 279 patients (15.1%) without renal dysfunction (p = 0.08).

In the univariate analysis using the Kaplan-Meier method, patients with renal dysfunction had a significantly greater likelihood of sudden death (log-rank p = 0.034) (Figure 3) and the combined end point of sudden death or potentially lethal arrhythmic events (log-rank p <0.001) (Figure 3) than those without renal dysfunction. A multivariable analysis that included the age and sex (model 1), established the risk factors for sudden death (model 2) and highly imbalanced baseline variables (model 3), showed that renal dysfunction (Table 2) and a decline in the GFR per 10 ml/min (Table 2) were independently associated with the combined end point of sudden death or potentially lethal arrhythmic events.

Table 1
Baseline characteristics of the HC patients with renal dysfunction (eGFR <60 ml/min/1.73 m^2) and without renal dysfunction (eGFR ≧60 ml/min/1.73 m^2)

Variable	All patients(N = 450)	Renal dysfunction		p value
		YES (N = 171)	No (N = 279)	
Age at the time of the initial evaluation (years)	53 ± 14.1	57 ± 11.7	51 ± 15.0	<0.001
Male sex	293 (65%)	96 (56%)	197(71%)	0.002
Outflow tract obstruction	103 (23%)	43 (25%)	60 (22%)	0.37
Hypertension	195 (43%)	78 (46%)	117 (42%)	0.45
Diabetes mellitus	79 (18%)	27 (16%)	52 (19%)	0.44
Coronary heart disease	31 (7%)	12 (7%)	19 (7%)	0.93
Atrial fibrillation	126 (28%)	54 (32%)	72 (26%)	0.20
Family history of sudden cardiac death	57 (13%)	20 (12%)	37 (13%)	0.63
Nonsustained ventricular tachycardia	171(38%)	72 (42%)	99 (36%)	0.16
Unexplained syncope	79 (18%)	35 (21%)	44 (16%)	0.20
New York Heart Association functional class				0.01
I	227 (50%)	71 (42%)	156 (56%)	
II	200 (44%)	87 (51%)	113 (41%)	
III	23 (5%)	13 (8%)	10 (4%)	
Maximum left ventricular wall thickness (mm)	19 ± 4.9	18 ± 4.8	19 ± 5.0	0.15
E/e' at the septal mitral annulus	16 ± 7.1	17 ± 7.4	15 ± 6.9	0.03
Left ventricular fractional shortening (%)	37 ± 9.0	35 ± 10.3	38 ± 8.0	0.005
Left atrial dimension (mm)	40 ± 8.4	41 ± 8.7	39 ± 8.1	0.10
Resting heart rate (/min)	68 ± 11.5	68 ± 12.4	68 ± 10.8	0.98
QRS duration (milliseconds)	110 ± 27.5	115 ± 30.7	106 ± 24.9	0.002
RV5 (mm)	23 ± 14.0	24 ± 14.1	23 ± 14.0	0.38
Treatment				
β-blockers	315 (70%)	114 (67%)	201 (72%)	0.23
Renin-angiotensin-aldosterone system blockers	167 (37%)	61 (36%)	106 (38%)	0.62
Amiodarone	55 (12%)	27 (16%)	28 (10%)	0.07

All data are expressed as the mean ± SD, n (%).

HC = hypertrophic cardiomyopathy; eGFR = estimated glomerular filtration rate. E = early transmitral filling velocity; e' = early diastolic mitral annular velocity.

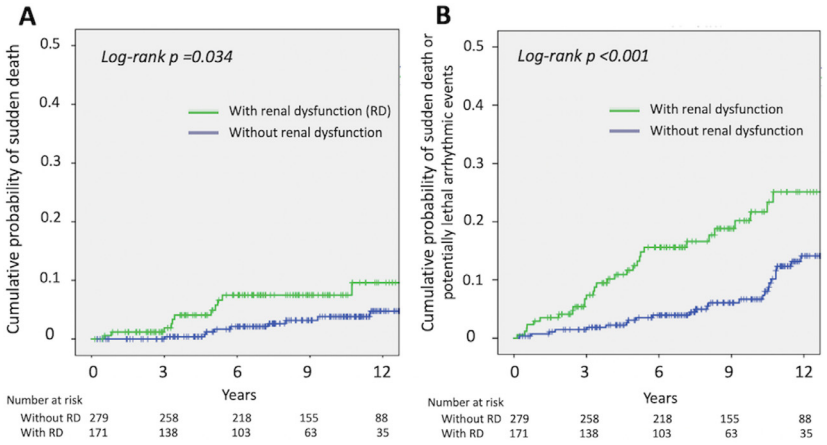

Figure 3. Kaplan-Meier estimates of the proportions of patients with sudden death and the combined end point of sudden death or potentially lethal arrhythmic events in the HC patients. Cumulative probability of *(A)* sudden death and *(B)* the combined end point of sudden death or potentially lethal arrhythmic events in the HC patients with and without renal dysfunction (eGFR <60 ml/min/1.73 m^2). eGFR = estimated glomerular filtration rate; HC = hypertrophic cardiomyopathy.

Discussion

Renal dysfunction is a common co-morbidity in patients with organic heart disease. According to the previous large studies in patients with ischemic heart disease, the prevalence of renal dysfunction (eGFR <60 ml/min/1.73 m^2) was 24% to 63%.[6–8] Another report showed that among 47,282 patients with a primary prevention ICD placement, 45% of the patients had renal dysfunction.[14] In our HC cohort, renal dysfunction was found in 38%, which seemed to be similar to the previous studies. Lee et al. recently reported the risk of end-stage renal disease in patients with HC. In their report, the prevalence of renal dysfunction was 17%, which was relatively lower than that in our report.[9] Though the discrepancy between their studies and our study remains unclear, it may have been caused by our data having been from a cohort from tertiary centers for HC patients and the latter was data from a nationwide population-based cohort. Furthermore, the end point in our study, the incidence of sudden death, was 0.5% per year, confirming the results of the previous studies that reported sudden death rates of 0.2% to 0.7% per year in patients with HC.[3] Therefore, the results of this study may have consistency and generalizability, providing additional epidemiological information on renal dysfunction and the sudden death rate in a relatively large longitudinal cohort of patients with HC.

Table. 2
Adjusted hazard ratios for the combined end point of sudden death or potentially lethal arrhythmic events

(A) Presence of renal dysfunction				
Independent variable	Model type	Hazard ratio	95% Confidence interval	p Value
Without renal dysfunction	Reference	1.00		
With renal dysfunction	Univariable	2.64	1.55−4.48	<0.001
	Model 1*	3.08	1.76−5.39	<0.001
	Model 2†	2.99	1.70−5.27	<0.001
	Model 3‡	2.04	1.10−3.79	0.024
(B) Per 10 ml/min decline in the eGFR				
Independent variable	Model type	Hazard ratio	95% Confidence interval	p Value
eGFR ≧90 ml/min/1.73 m^2	Reference	1.00		
Per 10 ml/min decline	Univariable	1.29	1.11−1.49	0.001
	Model 1*	1.36	1.17−1.57	<0.001
	Model 2†	1.35	1.15−1.58	<0.001
	Model 3‡	1.24	1.04−1.47	0.013

eGFR = estimated glomerular filtration rate.

* Model 1 was adjusted for the age (at the time of the initial evaluation) and sex.

† Model 2 was adjusted for the age, sex, and established risk factors for sudden cardiac death (the maximum left ventricular wall thickness, family history of sudden death, unexplained syncope, and non-sustained ventricular tachycardia).

‡ Model 3 was adjusted for the age, sex, and highly imbalanced baseline variables (New York Heart Association functional class, left ventricular fractional shortening, E/e' at the septal mitral annulus and QRS duration).

There have been numerous studies demonstrating a linear relation with a negative slope between the eGFR and SCD risk in patients with ischemic heart disease.[6–9] On the contrary, there have been limited data regarding the association between renal dysfunction and the SCD risk in nonischemic heart disease. In the present study, we found that the HC population may also have the same negative slope as could be seen in those with ischemic heart disease. Though the underlying mechanism of renal dysfunction and the SCD risk in patients with HC remains unclear, there are some possible explanations. First, renal dysfunction causes the activation of the sympathetic nervous system and renin-angiotensin system, and electrolyte abnormalities may provoke an exaggerated inflammatory response to the myocardium and alter the myocardial structure rendering a proarrhythmic state.[15] In our study, patients with renal dysfunction had a higher septal E/e' than those without renal dysfunction. Theoretically, a stiff LV might increase the LV filling pressure and renal venous pressure through activation of the renin-angiotensin system, and facilitate an unfavorable volume distribution, and consequently a disturbed renal function.[16] Second, our study patients with renal dysfunction had a worse NYHA functional class than those without renal dysfunction. The NYHA functional class has been incorporated as a parameter to guide the placement of ICDs for primary prevention of SCD in nonischemic cardiomyopathy.[17] A volume and pressure overload may increase the risk of SCD.

Some limitations must be taken into account when interpreting this study. First, this study relied on the serum creatinine, based on a clinically available test of the renal function. Therefore, a direct measure of the glomerular filtration rate (iothalamate clearance) or cystatin C level, an alternate indirect measurement of the kidney function may have detected a stronger or more linear association. Second, this was a single-center observational study with a retrospective enrollment of individual patients with HC, making it difficult to establish any causal relations. Therefore, further population-based, multicenter, and multinational studies are required to confirm and extend our findings. Third, despite adjustments by multivariable analyses, we cannot completely exclude the possibility of residual confounding factors of the association between renal dysfunction and the combined end point of sudden death or potentially lethal arrhythmic events by the unmeasured variables. Furthermore, in our multivariate analysis, sudden deaths, nonfatal or resuscitated cardiac arrests, and appropriate ICD interventions were considered to be equivalent, however, defibrillator interventions were not fully equivalent to sudden deaths.

In conclusion, renal dysfunction may be associated with the risk of sudden death and potentially lethal arrhythmic events in patients with HC. Our results suggest that an early risk stratification and active surveillance of the renal function may be favorable in the HC population.

Disclosures

The authors have no conflict of interest to disclose. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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