

Research Letter

Chronic Heart Failure Is Infrequently Associated With Renal Dysfunction in Hypertrophic Cardiomyopathy

It is estimated that about 50% of patients with chronic congestive heart failure develop progressive renal dysfunction, often termed the cardiorenal syndrome, a complication associated with increased mortality.^{1,2} Drug-refractory advanced heart failure in hypertrophic cardiomyopathy (HCM) has become an increasingly prominent management issue.³ However, the mechanisms responsible for heart-failure symptoms in HCM differ distinctly from more the common forms of congestive heart failure,^{3,4} and mortality risk is substantially lower.³ These observations raise the relevant questions of how commonly renal dysfunction and end-stage disease occur and are clinically important for the progression of heart failure in HCM.

Therefore, we examined the presence and significance of renal dysfunction in 371 consecutive patients with severely symptomatic HCM heart failure (94% in New York Heart Association [NYHA] class III/IV) who were undergoing invasive hemodynamic studies. The duration of symptoms prior to the invasive study was 11 ± 10 months, and patients were followed for 3.2 ± 2.7 years after the invasive study (up to 11 years). Patients with and without renal dysfunction were compared so as to determine potential differences in clinical features and outcomes. The Student t test or the Wilcoxon rank-sum test addressed the statistical significance of continuous variables; the chi-square or the Fisher exact test was used to test categorical variables. For patients with known survival and event status, the fraction at each follow-up interval was estimated by the Kaplan-Meier method. Patients who had not experienced cardiovascular events at their most recent contacts were censored in the analysis. Differences in survival or clinical events between patient groups were assessed using the log-rank test.

Renal dysfunction (defined as estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73m²) was present in only 24 patients with heart failure (6%; eGFR 30 to 59 in 21), much less common than has been reported in congestive heart failure (ie, up to 50%).^{1,2} The occurrence of renal dysfunction in HCM was notably similar to that expected in the general U.S. population.⁵ Renal dysfunction was no more common in patients with obstructive than nonobstructive HCM (6% vs 8%; $P = 0.60$).

Furthermore, end-stage renal disease (eGFR < 15 mL/min/1.73m² and/or requiring dialysis or transplant) was absent over the follow-up period in each of 296 patients with heart failure secondary to outflow obstruction, and it developed in only 2 of 75 patients (3%) with nonobstructive disease.

In sharp contrast to that reported for non-HCM congestive heart failure, in our HCM cohort, heart failure-related mortality was uncommon, occurring in just 14 (3.8%) of 371 patients (1.3%/year). Renal dysfunction does not appear to be associated with HCM-related mortality or adverse clinical events, given that there was no significant difference in number of deaths from heart failure, heart transplantation or arrhythmic sudden-death events in patients with or without renal dysfunction over follow-up ($P = 0.63$, $P = 0.82$ and $P = 0.58$).

Low HCM-heart failure mortality may have, in part, been driven by the effectiveness of surgical myectomy (or alcohol ablation) in relieving LV outflow gradient and symptoms; patients with and without renal dysfunction experienced similar improvement to NYHA classes I/II (89% vs 94%, $P = 0.61$) after operative relief of obstruction.

We found no obvious cardiac-related mechanism responsible for renal dysfunction in patients with HCM. Specifically, patients with and without renal dysfunction showed no clear statistical difference in NYHA functional class, left ventricular (LV) wall thickness, magnitude of LV outflow obstruction, ejection fraction, or duration of symptoms ($P = 0.1-0.9$) (Table 1). Furthermore, hemodynamic abnormalities did not differ significantly between patients with

Table 1. Demographic and Clinical Variables of 371 Severely Symptomatic Patients With HCM by GFR

Variable	GFR ≥ 60 (n = 347; 94%)	GFR < 60 (n = 24; 6%)	P value
Male	170 (49%)	11 (46%)	0.76
Age at diagnosis (years)	48 ± 15	58 ± 14	0.004
Age at evaluation (years)	57 ± 13	65 ± 9	<0.001
Renal dysfunction			
Stage III (eGFR 30–60 mL/min/1.73m ²)	—	21 (87%)	
Stage IV (eGFR 15–29 mL/min/1.73m ²)	—	3 (13%)	
Stage V (eGFR 1–14 mL/min/1.73m ²)	—	0	

(continued)

Table 1 (Continued)

Variable	GFR \geq 60 (n = 347; 94%)	GFR < 60 (n = 24; 6%)	P value
Ejection fraction, %	62 \pm 11	58 \pm 15	0.11
Ejection fraction < 50%, n (%)	32 (9%)	4 (17%)	0.27
LV end diastolic dimension (mm)	41 \pm 7	39 \pm 10	0.10
Left atrial dimension (mm)	43 \pm 8	43 \pm 8	0.87
Maximal LV wall thickness (mm)	19 \pm 4	18 \pm 5	0.36
LV wall thickness \geq 30 mm, n (%)*	13 (4%)	0	1.0
LVOT gradient \geq 30 mm Hg at rest, n (%)	186 (53%)	15 (63%)	0.40
LVOT gradient < 30 mm Hg at rest and \geq 50 mm Hg with exercise, n (%)	92 (27%)	3 (12%)	0.25
Nonobstructive HCM, n (%)	69 (20%)	6 (25%)	0.60
Syncope, n (%)	58 (17%)	1 (4%)	0.15
Nonsustained ventricular tachycardia on ambulatory 24–48-hour monitor, n (%)	43 (12%)	0	0.12
Family history of sudden death, n (%)	30 (9%)	1 (4%)	0.70
ICD, n (%)	135 (39%)	7 (29%)	0.36
Atrial fibrillation, n (%)	124 (36%)	15 (65%)	0.01
Hypertension, n (%)	129 (37%)	14 (58%)	0.04
Diabetes, n (%)	33 (10%)	3 (12%)	0.72
COPD, n (%)	25 (7%)	7 (29%)	<0.001
Prior cancer history, n (%)	38 (11%)	2 (8%)	1.0
BMI (kg/m ²)	32 \pm 7	33 \pm 7	0.25
NYHA class at evaluation, n (%)			
Class I	0	0	0.49
Class II	25 (7%)	1 (4%)	
Class III/IV	322 (93%)	23 (96%)	
Right atrial pressure (mm Hg)	9 \pm 5	11 \pm 8	0.20
Right atrial pressure \geq 10 mm Hg, n (%)	127 (36%)	12 (50%)	0.19
Mean pulmonary artery pressure (mm Hg)	28 \pm 10	33 \pm 12	0.06
Mean pulmonary artery pressure \geq 30 mm Hg, n (%)	128 (37%)	13 (54%)	0.09
Pulmonary artery wedge pressure (mm Hg)	17 \pm 8	21 \pm 12	0.15
Mean pulmonary artery wedge pressure \geq 20 mm Hg, n (%)	112 (32%)	12 (50%)	0.08
Cardiac index (L/min/m ² ; Fick method)	2.5 \pm 0.6	2.3 \pm 0.5	0.04
Cardiac index < 2.2 L/min/m ² , n (%)	128 (37%)	13 (54%)	0.32
eGFR (mL/min/1.73m ²)	86 \pm 15	43 \pm 9	<0.001
Blood urea nitrogen (mg/dL)	16 \pm 5	31 \pm 14	<0.001
Creatinine (mg/dL)	0.9 \pm 0.2	1.6 \pm 0.5	<0.001
Blood urea nitrogen to creatinine ratio	19 \pm 6	19 \pm 5	0.56
Sodium (mEq/L)	140 \pm 3	139 \pm 2	0.21
Chloride (mEq/L)	106 \pm 4	104 \pm 4	0.10
Bicarbonate (mEq/L)	26 \pm 3	25 \pm 2	0.15
Hemoglobin (g/dL)	13.5 \pm 1.7	12.7 \pm 2.4	0.11
Medications, n (%)			
β -blockers	274 (79%)	16 (67%)	0.20
Calcium channel blockers	103 (30%)	6 (25%)	0.66
ACE/ARB	78 (22%)	8 (33%)	0.22
Loop diuretics	71 (20%)	10 (42%)	0.02
Furosemide dose*	85 \pm 85	135 \pm 112	0.20
Sudden death events, n (%)			
Appropriate ICD interventions [†]	18 (5%)	1 (4%)	1.0
Resuscitated cardiac arrest [‡]	2 (1%)	0	1.0
Outcome			
Septal myectomy, n (%) [†]	216 [†] (62%)	11 (46%)	0.11
Alcohol septal ablation, n (%) [‡]	73 [‡] (21%)	8 (33%)	0.09
Listed for transplant, n (%)	36 (9%)	3 (12%)	0.73
Heart transplant	23 (7%)	1 (4%)	1.0
Death awaiting transplant	6 (<1%)	1 (4%)	0.38
Active on transplant list	7 (2%)	1 (4%)	0.42
Death, n (%)			
Non-HCM death	19 (6%)	3 (12%)	0.16
HCM death	13 (4%)	1 (4%)	0.63
Sudden death	0	0	—
Heart-failure death	9 (3%)	1 (4%)	0.50
Postop death	1 (<1%)	0	1.0
Post-transplant death	3 (1%)	0	1.0

BMI, body mass index; COPD, chronic obstructive lung disease; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; LV, left ventricular; LVED, left ventricular end-diastolic dimension; LVOT, left ventricular outflow tract; NYHA, New York Heart Association.

*Furosemide or equivalent loop diuretic dose.

[†]Includes 2 patients with subsequent secondary prevention appropriate ICD interventions.

[‡]Includes 14 patients with unsuccessful alcohol ablation prior to surgical myectomy.

Note: Values are mean \pm standard deviation or number (% of subjects), when applicable.

and without renal dysfunction: elevations in right atrial (≥ 10 mm Hg; 50% vs 36%; $P = 0.19$), mean pulmonary artery (≥ 30 mm Hg; 54% vs 37%; $P = 0.09$), and pulmonary capillary wedge pressure (≥ 20 mm Hg; 50% vs 32%, $P = 0.08$) or decreased cardiac index (< 2.2 L/min/m²; 54% vs 37%; $P = 0.32$).

Alternatively, our data suggest that noncardiac factors likely contribute to renal dysfunction in HCM. For example, patients with HCM and renal dysfunction were older (65 ± 9 vs 57 ± 13 years; $P = < 0.001$) and more commonly had comorbidities (including systemic hypertension and chronic obstructive pulmonary disease) compared to patients without renal dysfunction ($P = 0.04$ and < 0.001) (Table 1). However, we cannot exclude the possibility that diuretic therapy contributed to renal impairment, given that the level of diuretic administration significantly exceeded that for patients without renal dysfunction (42% vs 20%; $P = 0.02$). It should be noted that although we found no obvious associations between morphologic or hemodynamic abnormalities and renal dysfunction in our patients with HCM, the infrequency of renal dysfunction in our cohort limits our power to make definitive conclusions regarding mechanism.

The adaptive mechanism responsible for the infrequency of renal dysfunction and end-stage disease in patients with HCM-related heart failure is undefined. Nevertheless, this is a clinical situation that may well contribute to low HCM-related mortality, perhaps not dissimilar to other undefined mechanisms in HCM, such as protection in heart failure from pulmonary and peripheral edema and volume overload.³

In conclusion, in HCM, long-standing progressive heart failure rarely results in renal dysfunction and end-stage renal disease (cardiorenal syndrome) a feature of the disease that is highly favorable for its natural history; this is reassuring to symptomatic patients and is a major distinguishing feature from non-HCM congestive heart failure. Renal dysfunction in HCM appears to be secondary to comorbidities in older patients and less likely to result from HCM-related hemodynamic abnormalities. The rarity of cardiorenal syndrome probably contributes significantly to the low mortality associated with heart failure in HCM.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.cardfail.2019.05.012](https://doi.org/10.1016/j.cardfail.2019.05.012).

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