Advanced Heart Failure With Preserved Systolic Function in Nonobstructive Hypertrophic Cardiomyopathy

Under- Recognized Subset of Candidates for Heart Transplant

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Background—In hypertrophic cardiomyopathy (HCM), heart transplant has been predominantly confined to patients with systolic dysfunction. An underappreciated HCM subset comprises patients with preserved left ventricular (LV) systolic function who may also require consideration for transplantation. Therefore, we sought to define the clinical profile and occurrence of advanced heart failure among patients with nonobstructive HCM and preserved systolic function.

Methods and Results—Databases from 2 referral centers comprising 2100 HCM patients were interrogated. Forty-six nonobstructive HCM patients (2.2%) either received or were listed for heart transplant, including 20 with normal systolic function (ejection fraction ≥50%). At transplant listing, these 20 patients were 42±13 years old, each in New York Heart Association functional class III/IV with ejection fraction of 62±7%. LV was hypertrophied with maximum wall thickness of 22±4 mm and nondilated (end-diastolic dimension, 39±7 mm). Cardiovascular magnetic resonance in 10 (of 15) patients showed no or minimal fibrosis (≤5% LV mass). Elevated LV end-diastolic or pulmonary capillary wedge pressure, consistent with diastolic dysfunction, was present in 15 patients (75%). LV filling was impaired by echocardiographic measures in all patients, including a restrictive inflow pattern in 8 (40%). In 2 patients, traditional criteria for transplant were absent, including peak VO2 >14 mL/kg/min. Heart transplantation was performed in 12 patients with each alive and without cardiovascular symptoms, 2.3±1.7 years later.

Conclusions—A previously under-recognized segment of the broad HCM clinical spectrum consists of nonobstructive patients with advanced heart failure, in the presence of preserved systolic function, for whom heart transplant is the sole definitive therapeutic option. (Circ Heart Fail. 2014;7:967-975.)

Key Words: diastolic dysfunction ■ heart transplantation ■ hypertrophic cardiomyopathy

Sudden death has perhaps been the most visible adverse consequence of hypertrophic cardiomyopathy (HCM). However, with the increased use of the implantable cardioverter defibrillator for primary prevention, heart failure progression and death are emerging prominently within the natural history of HCM and with regard to strategies for disease management. In this regard, heart transplantation has, by convention, been confined predominantly to those HCM patients evolving into the end-stage phase, characterized by left ventricular (LV) systolic dysfunction (ejection fraction [EF] <50%). However, within the diverse HCM phenotypic spectrum, we have recently recognized a subgroup of nonobstructive patients with severe drug-refractory heart failure symptoms, but nevertheless have preserved LV systolic function; without other therapeutic options, these patients become candidates for heart transplant. Therefore, we take this opportunity to characterize the presentation, clinical profile, and outcome of this largely under-recognized subset within the HCM patient population.

Clinical Perspective on p 975

Patient Selection

HCM patient databases of 2 referral centers, Minneapolis Heart Institute Foundation (Minneapolis, MN) and Tufts Medical Center (Boston, MA), were accessed. Patients with HCM who had undergone heart transplant or were listed for transplant (2004–2013) were included. Patients who met the following criteria constitute the preserved LV systolic function study population: (1) EF ≥50%; (2) New York Heart Association (NYHA) functional class III/IV, refractory to maximum medical management; (3) LV outflow gradient <30 mm Hg.
at rest and with physiological (exercise) provocation. Patients with LV outflow obstruction who underwent septal reduction therapy and subsequently developed advanced heart failure were excluded (n=7).
Initial clinical evaluation was the first clinical assessment obtained at either participating institution. Transplant listing was defined as date of acceptance on the UNOS (united network for organ sharing) heart transplant list. Most recent evaluation was obtained during clinic visit or by telephone interview. This study has been reviewed and approved by Institutional Review Boards of the participating institutions, Allina Health Systems and Tufts Medical Center, permitting use of patient medical information for research. All authors had full access and took responsibility for integrity of the data and agreed to the article as written.

Definitions

HCM Diagnosis
HCM diagnosis was made by echocardiographic and cardiovascular magnetic resonance (CMR) documentation of a hypertrophied and nondilated left ventricle (wall thickness ≥15 mm in adults), at some time during their clinical course, in the absence of another cardiac or systemic disease capable of producing a similar magnitude of hypertrophy.

Heart Failure
Advanced heart failure was defined as symptom limitation to New York Heart Association (NYHA) functional class III or IV, characterized predominately by exertional dyspnea (with or without chest pain). Global LV systolic dysfunction (by convention, end-stage HCM) was arbitrarily defined by EF <50% at rest.
Patients with EF ≥50% were designated as preserved LV systolic function.

Echocardiography
Transsthoracic echocardiographic studies were performed with commercially available instruments 2.5±1.1 months before transplant listing. Magnitude of LV hypertrophy, left-atrial, and LV end-diastolic dimensions were obtained as previously described. Mitral regurgitation was graded as mild, moderate, or severe by combined analysis of jet area, width, and spectral Doppler intensity. EF was calculated from 2-dimensional echocardiographic images with the modified Simpson rule formula or area-length method.
LV outflow tract obstruction because of systolic anterior motion of the mitral valve with septal contact was imaged in the apical views with continuous wave Doppler. Patients without an LV outflow gradient under basal conditions underwent exercise echocardiography performed with symptom-limited Bruce protocol. LV outflow tract gradient was reassessed immediately after exercise.
Mitral inflow velocity and annular tissue Doppler indices signals were obtained, as previously described. Peak pulsed Doppler velocities were assessed to determine early (E) and late (A) diastolic flow across the mitral valve. Tissue Doppler index of the mitral annulus was calculated from the apical 4-chamber view, and peak early tissue Doppler velocities of the septal mitral annulus (e') were analyzed. Diastolic dysfunction was classified according to previous consensus recommendations. Echocardiographic measures of diastolic function were not assessed in 2 patients because of presence of atrial fibrillation at the time of study.

Cardiovascular Magnetic Resonance
CMR studies were performed with a 1.5 Tesla clinical CMR scanner in 15 patients, while 5 patients did not undergo CMR examination because of a previously implanted implantable cardioverter defibrillator. Breath-hold cine steady state free precession sequences were performed in horizontal long axis, vertical long axis, and contiguous short axis slices with full coverage of LV and slice thickness of 10 mm with no gap. Short-axis cine stack was obtained parallel to atrioventricular groove, covering the entire LV chamber. Late gadolinium enhancement (LGE) images were acquired 10 to 15 minutes after intravenous administration of 0.2 mmol/kg gadolinium-DTPA (Magnevist, Schering; Berlin Germany) using breath-held segmented inversion recovery sequence acquired in same orientations as the cine images. The LV short-axis stack of LGE images was first assessed visually for presence of LGE. Quantification of LGE was then performed on all LGE-positive studies by manually adjusting a grayscale threshold to define areas of visually identified LGE. These areas were then summed to generate a total volume of LGE and expressed as a proportion of total LV myocardium (%LGE).

Cardiopulmonary Stress Test
Cardiopulmonary stress testing was performed in 17 patients with symptom-limited erect treadmill exercise testing using a standard ramp protocol with simultaneous respiratory gas analysis. Peak oxygen consumption (VO2) was defined as the maximum VO2 achieved during exercise, expressed in ml/min/kg. Predicted % VO2 relative to patient age and sex was calculated according to established guidelines.

Invasive Hemodynamics
Hemodynamic studies were performed on cardioactive medications, 1.9±3.1 months before transplant listing. Right atrial, pulmonary artery, pulmonary capillary pressures, and LV end-diastolic pressures were measured at end expiration and taken as the average of 23 beats. Cardiac output was determined by the Fick method using directly measured saturations and oxygen consumption and indexed to body surface area (cardiac index).
Hemodynamic measurements were obtained with exercise in 3 patients in whom LV filling pressures were normal under resting conditions (mean PA pressure ≤25 mm Hg and PCWP ≤15 mm Hg), and peak VO2 was >14 ml/min/kg. An exercise protocol was performed by outstretched arm adduction lifting of 4 pound weights until fatigue, with hemodynamic parameters measured after peak exercise and at 1 minute recovery.

Statistical Analysis
Data are displayed as means±SD for continuous variables and as proportions for categorical variables. Student’s t test or Wilcoxon rank-sum test assessed statistical significance for continuous variables and χ2 or Fisher’s exact tests for categorical variables. P values <0.05 were considered significant and 2-sided where appropriate. Statistical analyses were performed with SAS for Windows version 9.3 (SAS Institute Inc, Cary, NC).

Results

Prevalence, Demographics, and Clinical Profile
Of the 2100 HCM patients in the cohort, 46 (2.2%) had been transplanted, listed for transplant, or died while awaiting transplantation. Of these 46 patients, 26 (1.2%) had systolic dysfunction (EF <50%) and were considered to be in the end-stage phase of HCM, while the other 20 patients (1.0%) had preserved EF ≥50% and constitute the study group (prevalence, 9.5 per 1000 HCM patients; Figure 1 and Table 1).
Among the 20 study patients (11 men), initial HCM diagnosis was at 32±15 years of age (range 12–61) and onset of heart failure symptoms at 35±16 years (Figure 2). Patients were listed for transplant at 42±13 years (range 16–66; Tables 2 and 3). Duration between symptom onset and listing was 8.0±8.9 years, including 6 patients listed <2 years after symptom onset and 9 patients ≥5 years after symptoms developed.
Among the 20 nonobstructive HCM patients with preserved LV systolic function, 12 underwent transplant at a mean age of 42±16 years (220±181 days after listing), including 4 patients <30 years of age, 5 patients between 40 and 49 years, and 3 patients >50 years. Time on the waiting list before transplantation ranged from 21 to 615 days (mean, 0.6±0.5 years).
In 14 of the 20 patients, ≥1 family member was known to have HCM, including 5 (25%) with a first-degree relative who developed end-stage HCM (EF=34±2%). Two of the family
members in the end-stage (mothers of patients Nos. 6 and 8) required heart transplant at 51 and 58 years of age, respectively, whereas the remaining 3 relatives in end-stage are alive, symptomatic, but without transplant.

A variety of pathogenic sarcomeric protein mutations were identified in 6 of 9 patients who underwent genetic testing: MYH7 (n=3), ACTC1 (n=1), TNNI (n=1), and TPM1 (n=1; Tables 2 and 3), including 1 patient with a family member in end-stage phase who underwent cardiovascular magnetic resonance.

Phenotypic Expression

Based on echocardiography, CMR, and pathological examination of explanted hearts (n=8), each patient had a hypertrophied, thick-walled LV in the presence of a nondilated ventricular cavity. Maximum LV wall thickness (usually in ventricular septum) was 22±4 mm (range, 15–34 mm) by echocardiography, including 4 patients with 25 to 29 mm and 2 patients with massive hypertrophy, that is, ≥30 mm (Figures 1 and 3). LV cavity size was small, 39±7 mm end-diastolic dimension (range, 29–52 mm, and ≤40 mm in 10 patients). Left atrial diameter was 46±8 (range, 31–57 mm). EF was 62±7% (range, 55–70%), including 6 patients with an EF of 70% and 5 with EF of 55%.

Coronary artery patency was examined by arteriogram or CT angiography in 18 of 20 patients and by examination of the explanted heart in the other 2. Atherosclerotic coronary artery disease (ie., ≥50% luminal narrowing in ≥1 epicardial vessels) was absent in each patient. Three patients had a history of angina responsible for functional limitation, considered to be HCM-related.

**Hemodynamics**

Evidence of increased LV filling pressure, consistent with diastolic dysfunction, was present at cardiac catheterization.
under basal conditions in 15 patients (75%), including LV end-diastolic pressure >15 mm Hg in 5 patients (range, 20–30) and pulmonary capillary wedge pressure >15 mm Hg in 8 patients without left heart catheterization (>25 mm Hg in 6; Tables 2 and 3). In 2 patients, pressures were normal at rest, but increased substantially at peak exertion (wedge pressure, 26 and 28 mm Hg). With echocardiography, diastolic dysfunction was assessed in 13 patients in sinus rhythm, each with impaired LV filling patterns: restrictive (Grade III) in 8, pseudonormal (Grade II) in 3, and impaired relaxation (Grade I) in 2.

Of the 5 remaining study patients, each had normal LV filling pressures at rest. Invasive hemodynamic assessment with exercise was not performed in 4 (because of particularly severe functional limitation), and in 1 patient, LV filling pressures were normal at rest and with exercise. However, in each of these 5 patients, there was evidence of diastolic dysfunction by echocardiography (Grade I in 2 and Grade II in 3).

Pathology/Myocardial Fibrosis

Explanted Hearts

Native explanted hearts were available for gross and histological examination in 8 patients (Figure 1). Heart weight was increased in each (508±94 g in males and 418±61 g in females), including two >500 g. In each, histopathology showed cardiac muscle cell disorganization and abnormal

Table 2. Clinical and Demographic Data From 20 Patients With HCM and Preserved Systolic Function Listed for Heart Transplant

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<th>Patient</th>
<th>Gender</th>
<th>Age at TP Listing, y</th>
<th>Age at Dx, y</th>
<th>Age at 1st HF Symptoms, y</th>
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ACTC indicates α cardiac actin 1; Ch-AF, chronic atrial fibrillation; Dx, diagnosis; EF, ejection fraction; ES, end stage HCM; HCM, hypertrophic cardiomyopathy; HF, heart failure; LA, left atrium; LV, left ventricular; LVED, left ventricular end-diastolic dimension; MYH7, β myosin heavy chain; NSVT, nonsustained ventricular tachycardia; SD, sudden cardiac death; TNNI3, cardiac troponin I; TPM1, tropomyosin 1 α; and TP, transplant.

*Identical disease causing mutation identified in the patient’s father with end-stage HCM.

†Double mutation in MYH7 Arg719Trp, His581Arg (1 inherited from father, 1 from mother).
intramural coronary arteries typical of HCM. With gross and histopathologic examination, fibrosis was absent or minimal in 5 hearts (Figure 1), whereas moderate-to-extensive diffuse amounts of patchy nontransmural myocardial fibrosis was evident in ventricular septum and lateral wall of 3 hearts.

**Percent LGE**

Myocardial fibrosis was assessed by contrast-enhanced CMR in 15 patients (Figure 3). LGE was absent in 5 and present in 10 occupying 9±8% of LV mass (range 1.8%–21%), with 5 minimal and focal (<5% of LV mass) and 3 extensive/diffuse (>15% of LV mass).

**Atrial Fibrillation**

Atrial fibrillation was present in 12 patients, paroxysmal in 8 and persistent in 4. Attempts to restore and maintain sinus rhythm were unsuccessful with both electric cardioversion and antiarrhythmic drugs (ie, amiodarone [n=8], dofetilide [n=3], disopyramide [n=3], dronedarone [n=1], and sotalol [n=1]). In 7 patients, isolated pulmonary vein radiofrequency ablation was unsuccessful in restoring and maintaining sinus rhythm. Although heart failure symptoms were exacerbated in atrial fibrillation, all patients were in NYHA functional class III heart failure even when in sinus rhythm.

**Pharmacological and Mechanical Support**

Efforts to control heart failure symptoms and chest pain with drug treatment were unsuccessful in all patients, including administration of β-blockers and calcium channel blockers (n=20), diuretics (n=14), angiotensin-converting enzyme inhibitor or angiotension receptor blocker (n=7), aldosterone inhibitor (n=2), or ranolazine/nitrates (n=2). In addition, inotropic therapy (milrinone, n=7; combination milirinone and dobutamine, n=2) was administered to 9 patients. In-hospital support was necessary in 2 patients because of particularly unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Pleasanton, CA) for management of refractory cardiogenic shock with unstable hemodynamic profiles using an LV-assist device in 1 (Thoratec Percutaneous Ventricular Assist Device, Please...
Heart transplantation has traditionally been reserved largely for patients in the end stage of HCM, arbitrarily defined by EF <50%.2,9,15 In this regard, we have recently recognized a subset of nonobstructive HCM patients eligible for heart transplant because of severe, unrelenting heart failure symptoms refractory to pharmacological treatment, despite evidence of preserved LV systolic function. Therefore, we describe here the clinical profile and natural history of this under-recognized patient subset within the broad disease spectrum of HCM.

By interrogating the databases of 2 major HCM referral cohorts, we found that 2% of patients were listed for heart transplantation, and among these, more than 40% demonstrated a disease phenotype distinctly different from those nonobstructive patients eligible for heart transplant in the end-stage phase, characterized by impaired systolic function and often associated

Outcome

Twelve patients received a heart transplant and each is currently alive, without cardiovascular symptoms (NYHA functional class I), after 0.5 to 6.3 years (mean 2.3±1.7; Table I in the Data Supplement). In addition, after transplant, invasive hemodynamics parameters were significantly improved, including pulmonary capillary wedge pressure and cardiac index (P<0.001), without a significant change in EF (63±6% versus 62±4%; P=0.82; Table I in the Data Supplement). Six patients remain active on the transplant list as status 1B (n=1) or status 2 (n=5). Two patients died of unrelenting heart failure awaiting transplant.

Comparison of Patients With Preserved LV Systolic Function and End Stage

Compared with the study patients with preserved systolic function, those with EF <50% (end-stage) demonstrated evidence of adverse LV remodeling with increased cavity size (50±9 versus 39±7 mm; P<0.001), lesser degree of hypertrophy (wall thickness, 18±4 versus 22±4 mm; P=0.006), and a trend toward more extensive myocardial fibrosis on contrast-enhanced CMR (% LGE of LV myocardium, 18±10 versus 9±8; P=0.07; Table I and Figure 3). Particularly extensive fibrosis (LGE ≥15%) was present in 4 of 6 (67%) end-stage HCM patients compared with only 3 of 15 (20%) with preserved systolic function. Several relevant clinical variables were similar between the 2 subgroups, including peak VO₂, LV filling pressures, age at heart failure symptom onset, and time from onset of symptoms to transplant listing (Table 1).

Clinical Determinants of Heart Transplant Listing

In each of the 20 patients, the primary indication for transplant listing was a clinical history of disabling heart failure symptoms of exertional dyspnea (with or without chest pain), consistent with NYHA III/IV and refractory to optimal medical therapy. At least 1 additional clinical criteria supporting the need for transplantation was present in 18 patients, including (1) peak VO₂ ≤14 mL/min/kg or <50% predicted for age in 12 patients (Nos. 1–4, 7, 8, 12–14, and 16–18 in Tables 2 and 3); (2) unfavorable resting hemodynamic profile, including elevated LV filling pressures or impaired cardiac index, in 14 patients (Nos. 2–4, 6–9, 11, 12, 14, 16–18, and 20); and (3) acute hemodynamic deterioration requiring inotropic therapy or mechanical support in 10 patients (Nos. 1–3, 9, 11, 12, 15, and 17–19). Therefore, 5 patients had 1 additional supporting criteria for transplant, 8 patients had 2 criteria, and 5 had 3 supporting criteria.

In the remaining 2 patients, inotropic therapy or mechanical support was not required and other traditional criteria for transplant listing were absent, including peak VO₂ >14 mL/min/kg or ≥50% predicted for age and normal resting hemodynamic profile (patient Nos. 5 and 10). These patients were listed for transplant solely because of refractory disabling symptoms by history, judged secondary to HCM. In addition, 3 patients (No. 4, 13, and 14) were allowed exceptions by the regional transplant committee to obtain an advanced transplant status (ie., 1Ae or 1Be) than would otherwise be granted, given that traditional therapies that allow 1A or 1B listing criteria are generally not indicated in patients with HCM and preserved LV systolic function.2

Discussion

Advanced heart failure has become increasingly important among patients with HCM, given the capability of sudden death prevention afforded by the implantable cardioverter defibrillator.1–8 This evolving recognition underscores the importance of reliably identifying those HCM patients who may be candidates for major life prolonging heart failure therapies. Heart transplantation has traditionally been reserved largely for patients in the end stage of HCM, arbitrarily defined by EF <50%.2,9,15 In this regard, we have recently recognized a subset of nonobstructive HCM patients eligible for heart transplant because of severe, unrelenting heart failure symptoms refractory to pharmacological treatment, despite evidence of preserved LV systolic function. Therefore, we describe here the clinical profile and natural history of this under-recognized patient subset within the broad disease spectrum of HCM.

Figure 3. Cardiac MRI images of 3 nonobstructive hypertrophic cardiomyopathy patients with preserved systolic function and 1 patient in the end-stage phase with systolic dysfunction (EF<50%), each of whom either received heart transplant or are currently listed for transplant. A, Four-chamber long-axis image from a 41-year-old man genotyped to a pathogenic sarcomere mutation (TPM1 Glu 96 Asp) with normal systolic function (EF=70%), small LV cavity (end-diastolic diameter=29 mm), and septal thickness of 24 mm (asterisk; patient No. 7, Tables 2 and 3). B, Three-chamber long-axis image in a 63-year-old man with EF of 60% and ventricular septal hypertrophy (21 mm; asterisk) who required inotropic support with intravenous milrinone and dobutamine before heart transplant (patient No. 19). C, Four-chamber long-axis contrast-enhanced image demonstrating absence of late gadolinium enhancement (LGE; ie., fibrosis) in a 33-year-old woman with New York Heart Association functional class IV symptoms, currently status II listed for heart transplant (patient No. 5). D, Contrast-enhanced 4-chamber long-axis image in a 23-year-old man with end-stage hypertrophic cardiomyopathy: ejection fraction of 30%, LV end-diastolic cavity dimension of 53 mm, and extensive transmural LGE (arrow) occupying 21% of LV myocardial mass. Ao indicates aorta; LA, left atrium; LV, left ventricle; RA, right atrium; and RV, right ventricle.
with LV remodeling with regression of hypertrophy and ventricular chamber enlargement. In contrast, the novel subgroup reported here experienced progressive and advanced heart failure refractory to maximal medical management, despite demonstrating little or no evidence of LV chamber remodeling. For example, average LV wall thickness was 22 mm (up to 34 mm), and LV cavity dimensions were normal or small, typical of that encountered in the overall HCM disease spectrum. In addition, HCM transplant candidates with systolic dysfunction characteristically show diffuse (and often transmural) LV myocardial scarring grossly visible by examination of the explanted heart and also identifiable by contrast-enhanced CMR (ie, occupying on average almost 20% of total LV mass). However, in contrast, most of our patients with advanced heart failure and preserved systolic function showed no or minimal myocardial fibrosis.

However, despite these substantial differences in phenotypic expression, our study patients with normal systolic function became transplant candidates in the absence of any other available therapeutic option capable of restoring reasonable expectation for an improved and acceptable quality of life with increased functional capacity. Indeed, each transplanted patient has survived without significant transplant-related complications over a 6-year period and without residual cardiovascular symptoms. Indeed, survival after heart transplant for HCM patients has been shown to be similar (if not better) than that for patients with other cardiac diseases, with 75% and 61% survival 5- and 10-years post-transplant. This experience underscores the principle that nonobstructive HCM patients with advanced heart failure symptoms, refractory to medical therapies, can (and should be) considered for cardiac transplantation as a final therapeutic option, even in the presence of normal or hyperdynamic LV systolic function and substantial increase in LV mass.

We found no relevant clinical or imaging marker that adequately predicted risk for advanced heart failure in this subset of HCM patients. Nevertheless, a disproportionate number of probands (ie, 25%) reported here with preserved systolic function had a family history of end-stage HCM with reduced EF and LV remodeling, including 2 relatives who required heart transplant. That relatives within the same HCM family (and presumably with the same disease-causing mutation) progressed to transplant with distinctly different phenotypic expressions supports the principle that no definitive relationship has been established in HCM between individual sarcomere mutations and cardiac phenotype.

The predominant mechanism responsible for the progressive symptoms of heart failure experienced by the HCM patients reported here seems to be LV diastolic dysfunction. This view is supported by evidence of abnormal LV filling at rest (or with exercise) at cardiac catheterization and with echocardiography in each patient, and in the absence of other mechanisms known to produce heart failure in HCM, for example, LV outflow tract obstruction, marked mitral regurgitation, and associated atherosclerotic coronary artery disease. Notably, almost one half of our patients demonstrated a restrictive filling by echocardiography, previously shown to identify HCM patients at increased risk for progressive heart failure and transplant, independent of LV systolic function.

Nevertheless, we recognize that the decision to pursue transplant in this subset of HCM patients is complex and challenging and ultimately requires taking into account the individual clinical profile of the patient, with the greatest weight given to the clinical history and symptom profile. Indeed, 10% of our patients with preserved systolic function were considered for transplant even in the absence of traditional parameters, such as peak VO2 consumption ≤14 mL/kg/min, after recognition that transplant was the only therapeutic option with the capacity to restore an acceptable quality of life.

Our observations also have implications for current transplant listing criteria, which are based largely on an experience in patients with systolic heart failure and diseases other than HCM, principally ischemic and dilated cardiomyopathies. This underscores the need for clinicians familiar with HCM to participate closely with multidisciplinary heart failure/transplant team to ensure optimal treatment strategies are implemented for this unique subset of HCM patients, including appropriate candidacy for heart transplant.

Notably, the clinical course of HCM patients with advanced heart failure and preserved systolic function proved to be variable, and becoming transplant candidates at a broad range of ages (16–63 years), and at an average age of only 41 years. Furthermore, there were relatively modest time periods between onset of symptoms and listing for transplant (average, 8 years) and particularly between listing and the transplant itself (average, only 0.6 years). Therefore, these data underscore the importance of close longitudinal follow-up for nonobstructive HCM patients with limiting heart failure symptoms and a relatively high index of suspicion and low threshold to pursue cardiovascular evaluation for heart transplantation.

Several clinical studies and expert consensus guidelines in HCM have, by convention, arbitrarily considered an EF ≥50% to represent preserved systolic function, which served as the justification for choosing this specific EF cut point to identify our study cohort. However, most importantly, we recognize that HCM encompasses a broad range in EF (ie, from hyperdynamic to systolic dysfunction) expressing a continuum of cardiac systolic function and advanced heart failure because (1) some patients with preserved LV systolic function have relatives with HCM and systolic dysfunction, including transplant candidates; (2) several objective measures of advanced heart failure were similar between the 2 groups, including invasive measures of elevated LV filling pressures and level of functional limitation by cardiopulmonary exercise testing; and (3) a variability in the extent of myocardial fibrosis (LGE) evident by some patients with preserved LV systolic function showing substantial LGE and others with systolic dysfunction having minimal or no LGE.

The number of HCM patients considered for transplant with preserved LV systolic function in this study is small (n=20). This limitation is unavoidable given the infrequency in which this subset of patient occurs in this disease. Therefore, it is unlikely that prospective studies with substantially greater numbers of these particular patients will emerge in the near future.

In conclusion, we report a novel subgroup of patients with nonobstructive HCM, who developed advanced progressive heart failure and become transplant candidates, despite preserved systolic function and in the absence of significant LV remodeling. This emerging subgroup expands the spectrum of heart failure requiring transplant in HCM and includes...
patients with normal LV systolic function. The pathophysiologic determinant of this novel clinical course seems to be LV diastolic dysfunction. However, the severity of symptoms was not always supported by traditional heart transplant testing criteria, and the decision to offer transplant as a final therapeutic option should be made on an individual patient basis in the presence of advanced and refractory heart failure.

Disclosures

None.

References

Heart transplantation in hypertrophic cardiomyopathy (HCM) has traditionally been reserved for patients in the end-stage phase of this disease, arbitrarily defined by ejection fraction <50%. However, a novel subset of nonobstructive HCM patients become candidates for heart transplantation with severe, unrelenting heart failure symptoms refractory to pharmacological treatment, despite evidence of preserved left ventricular systolic function (ejection fraction ≥50%). We describe the clinical profile and natural history of this under-recognized patient subset within the broad disease spectrum of HCM, by assembling 20 such patients (1% of the general HCM cohort). We found no relevant clinical or imaging marker that adequately predicted risk for advanced heart failure with unrelenting symptoms in these patients, given their typical features indistinguishable from the general HCM population: left ventricular wall thickness 22±4 mm, left ventricular cavity nondilated (39±7 mm), and no or minimal fibrosis (<5% of left ventricular mass by cardiovascular magnetic resonance) in the majority of patients. Additionally, 10% of patients were considered for transplant even in the absence of other traditional transplant parameters, including peak VO₂>14 mL/kg/min, because transplant was the only therapeutic option with the capacity to restore an acceptable quality of life. These findings underscore the need for clinicians familiar with HCM to participate closely with multi-disciplinary heart failure teams to ensure that optimal treatment strategies are implemented in this unique subset of HCM patients, including, when appropriate, heart transplantation.
Advanced Heart Failure With Preserved Systolic Function in Nonobstructive Hypertrophic Cardiomyopathy: Under-Recognized Subset of Candidates for Heart Transplant

Ethan J. Rowin, Barry J. Maron, Michael S. Kiernan, Susan A. Casey, David S. Feldman, Katarzyna M. Hryniewicz, Raymond H. Chan, Kevin M. Harris, James E. Udelson, David DeNofrio, William C. Roberts and Martin S. Maron

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Supplemental Table 1: Clinical and Imaging Data Pre and Post-Heart Transplant in 12 Nonobstructive HCM Patients with Preserved LV Systolic Function

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time from TP to last follow up, yrs</th>
<th>NYHA class</th>
<th>RA pressure, mmHg</th>
<th>PA pressure S/D (mean), mmHg</th>
<th>PCWP, mmHg</th>
<th>Fick CO; CI, L/min; L/min/m²</th>
<th>LVED, mm</th>
<th>LA Dimension, mm</th>
<th>Max LV thickness, mm</th>
<th>EF, %</th>
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<td>9</td>
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**Abbreviations:** CI = cardiac Index; CO = cardiac output; EF = ejection fraction; LA = left atrium; LVED = LV end-diastolic dimension; NYHA: New York heart association; PA = pulmonary artery; PCWP = Pulmonary capillary wedge pressure; RA = right atrium; S/D: peak systolic/end diastolic; TP = transplant

**Symbols:**

*: Post-transplant invasive hemodynamic and echocardiographic data not available.