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Prevalence, Clinical Significance, and Genetic Basis of Hypertrophic Cardiomyopathy With Restrictive Phenotype

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Objectives The purpose of this study was to determine the prevalence, clinical significance, and genetic basis of hypertrophic cardiomyopathy (HCM) with "restrictive phenotype" characterized by restrictive filling and minimal or no left ventricular hypertrophy.

Background Hypertrophic cardiomyopathy is a heterogeneous myocardial disorder with a broad spectrum of clinical presentation and morphologic features. Recent reports indicated that some patients with restrictive cardiomyopathy, which is an uncommon condition defined by restrictive filling and reduced diastolic volumes with normal or near normal left ventricular wall thickness and contractile function, have features suggestive of HCM with mutations in cardiac troponin I, myocyte disarray at explant/autopsy, and relatives with HCM. Systematic evaluation of the restrictive phenotype in HCM patients has not been performed.

Methods We evaluated 1,226 patients from 688 consecutive HCM families to identify individuals who fulfilled diagnostic criteria for "restrictive phenotype."

Results Nineteen of 1,226 affected individuals (1.5%) from 16 families (2.3%) had the "restrictive phenotype." During follow up (53.7 ± 49.2 months), 17 patients (89%) experienced dyspnea (New York Heart Association functional class ≥2). The 5-year survival rate from all-cause mortality, cardiac transplantation, or implantable cardioverter-defibrillator discharge was 56.4%. Mutation analysis for 5 sarcomere genes was feasible in 15 of 16 probands. Mutations were found in 8: 4 in beta-myosin heavy chain, and 4 in cardiac troponin I.

Conclusions The "restrictive phenotype" in isolation is an uncommon presentation of the clinical spectrum of HCM and is associated with severe limitation and poor prognosis. This phenotype may be associated with beta-myosin heavy chain and cardiac troponin I mutations. (J Am Coll Cardiol 2007;49:2419–26) © 2007 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is a familial myocardial disorder caused by mutations in sarcomere protein genes (1–3). Although the mechanisms are not clear, these genetic alterations result in the characteristic pathological (myocyte disarray and fibrosis) and morphologic (hypertrophied, nondilated left ventricle) features of HCM (4).

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Diastolic abnormalities occur in the majority of patients with HCM and have long been recognized as a determinant of symptoms and exercise limitation (5–7). The diastolic abnormalities seen in the majority of patients are mild and consist of impaired relaxation and slow left ventricular (LV) filling, but some patients exhibit more severe diastolic abnormalities with rapid early filling and restrictive physiology. Recently, we reported a family with disease caused by a mutation in cardiac troponin I in which 12 individuals had typical HCM and 3 others exhibited a "restrictive phenotype" characterized by restrictive filling and minimal or no left ventricular hypertrophy (LVH), which (if seen in isolation) resembled idiopathic restrictive cardiomyopathy (RCM) (8,9). In addition, there are reports of patients who present clinically with typical features of RCM and are

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Abbreviations and Acronyms

CI = confidence interval
E/A = peak E-wave/A-wave velocity ratio
FS = fractional shortening
HCM = hypertrophic cardiomyopathy
ICD = implantable cardioverter-defibrillator
LV = left ventricular
LVEDD = left ventricular end-diastolic diameter
LVESD = left ventricular end-systolic diameter
LVH = left ventricular hypertrophy
MLVWT = maximum left ventricular wall thickness
MYBPC3 = cardiac myosin-binding protein C gene
MYH7 = beta-myosin heavy chain gene
RCM = restrictive cardiomyopathy
R-E = Romhilt-Estes
TNNI3 = cardiac troponin I gene
TNNT2 = cardiac troponin T gene
TPM1 = alpha-tropomyosin gene

found ultimately to have typical histopathological findings of HCM (10,11). Those patients could be diagnosed with HCM or RCM on another occasion. Although the "restrictive phenotype" may be part of the clinical spectrum of HCM, systematic evaluation of this "restrictive phenotype" in the context of HCM patients has never been performed. We focused on the gray zone (minimal or no LVH [maximum LV wall thickness (MLVWT) ≤15 mm] and severe diastolic dysfunction) between HCM and RCM where diagnosis may be problematic. The purpose of this study was to determine the prevalence, clinical characteristics, natural history, and genetic basis of HCM with "restrictive phenotype."

Methods

Study population. We systematically evaluated 1,226 patients with HCM from 688 families who were evaluated in a dedicated HCM clinic between 1988 and 2002. The diagnosis of HCM was based on either of the following criteria: 1) unexplained LVH (i.e., MLVWT ≥13 mm); or 2) unexplained electrocardiographic and/or echocardiographic abnormalities in the context of proven familial HCM with at least 1 relative who had an unequivocal diagnosis with conventional clinical or histopathological diagnostic features.

Patients with other causes of LVH such as Friedreich's ataxia, Noonan's syndrome, and primary metabolic disorders (e.g., Fabry disease, amyloidosis) were excluded.

Clinical evaluation. The evaluation of patients included medical history; clinical examination; pedigree analysis; 12-lead electrocardiography (ECG); ambulatory 48-h Holter ECG analysis; M-mode, 2-dimensional, and Doppler echocardiography; and maximal exercise testing with metabolic gas exchange measurements and continuous assessment of blood pressure response.

Patients were classified as "restrictive phenotype" on echocardiography if they fulfilled all of the following criteria: minimal or no LVH (MLVWT ≤15 mm), transmitral Doppler indexes of restrictive filling (peak E-wave/A-wave velocity ratio [E/A] ≥2 and deceleration time ≤150 ms), normal systolic function (fractional shortening [FS] ≥25%), and reduced or normal ventricular cavity size (left ventricular end-diastolic diameter [LVEDD] ≤ normal for age and body surface area) (12,13).

For survival analysis, 3 modes of HCM-related death were defined: 1) sudden and unexpected death (including resuscitated cardiac arrest), in which collapse occurred in the absence of or <1 h from the onset of symptoms in patients who previously experienced a relatively stable or uneventful clinical course; 2) heart failure-related death, which was in the context of progressive cardiac decompensation ≥1 year before death, particularly if complicated by pulmonary edema or evolution to the end-stage phase (including patients who had undergone heart transplantation); and 3) stroke-related death, which occurred as a result of probable or proven embolic stroke. In patients with implantable cardioverter-defibrillators (ICDs), the first appropriate shock was coded as an outcome in a separate survival analysis.

Data on survival and clinical status were obtained from patients with and without restrictive physiology during serial clinic visits or by direct communication with patients and their cardiologists for patients who were followed up at other institutions.

Echocardiography was performed using an Acuson 128 XP/10 (Mountain View, California), GE Vingmed system V (GE Ultrasound Europe, Horten, Norway) or a Hewlett-Packard Sonos 1000 (Hewlett-Packard, Andover, Massachusetts). Standard views for 2-dimensional and M-mode studies were obtained. The severity and distribution of LVH were assessed in the parasternal short-axis plane at mitral valve and papillary muscle levels (14,15). Maximum LV wall thickness was defined as the greatest thickness in any single segment. Left ventricular end-diastolic diameter and left ventricular end-systolic diameter (LVESD) were measured from M-mode and 2-dimensional images obtained from parasternal long-axis views, and FS (FS = 100 × [LVEDD − LVESD]/LVEDD) was calculated. Mitral inflow velocities were determined using pulse-wave Doppler with the sample volume positioned at the tips of the mitral leaflets in the 4-chamber view. Peak E-wave velocity (E), peak A-wave velocity (A), E/A ratio, and E-wave deceleration time were recorded. Left ventricular outflow tract gradient was calculated from continuous-wave Doppler using the simplified Bernoulli equation.

Patients underwent symptom-limited cardiopulmonary exercise testing on a bicycle ergometer (Sensormedics Ergometrics 800S, Bitz, Germany) using an incremental ramp protocol with respiratory gas sampling (V Max 29 Console, Sensormedics) and serial measurement of blood pressure during upright exercise. Peak oxygen consumption (V_{O_2}) was defined as the highest V_{O_2} achieved during exercise (16).

Genetic analysis. In patients identified as having restrictive phenotype, systematic mutation analysis for recognized HCM-causing genes was performed. Informed consent was obtained in accordance with the guidelines of the local institution's review committee. Peripheral blood samples were taken at the time of clinical evaluation, and they were

Table 1 Echocardiographic Characteristics of Patients at Initial Evaluation

	Patients With "Restrictive Phenotype" (n = 19)	Other HCM Patients (n = 1,207)	p Value
MLVWT, mm	13 ± 2.7 (7–15)	20 ± 6.3 (6–49)	<0.001
Left atrial diameter, mm	53 ± 4.5 (46–60)	43 ± 8.3 (19–75)	<0.001
LV end-diastolic diameter, mm	45 ± 4.7 (37–51)	44 ± 6.3 (22–65)	0.09
LV end-systolic diameter, mm	29 ± 5.1 (20–39)	25 ± 6.4 (10–45)	0.001
Fractional shortening, %	37 ± 6.4 (25–50)	43 ± 9.3 (9–72)	0.001
E/A	2.78 ± 0.60 (2.0–4.0)	1.44 ± 0.69 (0.4–6.0)	<0.001
DT, ms	115 ± 24 (70–148)	309 ± 182	<0.001
LVOTO, n (%)	0 (0%)	294 (24.3%)	0.006*

Data shown as mean ± SD (range) or n (%). *Fisher exact test was used.
DT = E-wave deceleration time; E/A = peak E-wave/A-wave velocity ratio; HCM = hypertrophic cardiomyopathy; LV = left ventricular; LVOTO = left ventricular outflow tract obstruction >30 mm Hg; MLVWT = maximum left ventricular wall thickness.

frozen and stored at −20°C. DNA was extracted. In vitro amplification of genomic DNA was performed using polymerase chain reaction. Sequencing was performed with a dye-terminator cycle sequence system and analyzed as previously described (8). In patients in whom a mutation was identified, confirmation was obtained by reanalysis with direct sequencing from a second blood sample.

Mutation analysis was carried out for the 5 most common sarcomere protein gene abnormalities: beta-myosin heavy chain (*MYH7*), cardiac myosin-binding protein C (*MYBPC3*), cardiac troponin T (*TNNT2*), cardiac troponin I (*TNNI3*), and alpha-tropomyosin (*TPM1*) genes.

Data analysis. Statistical analysis was performed using SPSS statistical software (version 10.0, SPSS Inc., Chicago,

Table 2 Clinical Characteristics of Patients With "Restrictive Phenotype"

	Patients With "Restrictive Phenotype" (n = 19)	Other HCM Patients (n = 1,207)	p Value
Age, yrs	42 ± 19	40 ± 17	0.6
Gender: male, n (%)	8 (42%)	740 (61%)	0.09
Age at diagnosis, yrs	38 ± 20	36 ± 17	0.5
Reason for diagnosis, n (%)			
Symptoms	11 (58%)	476 (39%)	0.2
Incidental findings	2 (10%)	292 (24%)	0.1
Family or gene screening	6 (32%)	307 (25%)	0.8
Age at onset of symptoms, yrs	38 ± 19	36 ± 16	0.5
Presence of symptoms (at presentation), n (%)	16 (84%)	764 (63%)	0.1
Dyspnea	12 (63%)	422 (35%)	0.01
Palpitation	6 (32%)	447 (37%)	0.4
Syncope	4 (21%)	144 (12%)	0.3*
Chest pain (exertional)	5 (26%)	444 (37%)	0.2
NYHA functional class (at presentation), n (%)			
I	7 (37%)	757 (63%)	0.01
II	9 (47%)	389 (32%)	0.2
III and IV	3 (16%)	33 (3%)	0.02*
NYHA functional class (at last evaluation), n (%)			
I	2 (11%)	513 (43%)	<0.00001
II	9 (47%)	258 (21%)	0.1
III and IV	8 (42%)	41 (3%)	0.00001*
Edema (by history), n (%)	8 (42%)	NA	NA
Abdominal discomfort, n (%)	3 (16%)	NA	NA
Exercise tolerance			
Peak Vo_2, ml/kg/min	17.3 ± 6.1	26.3 ± 9.7	<0.0003
Peak Vo_2, % Vo_2 max	49 ± 15	72 ± 21	0.00004
History of AF (chronic and paroxysmal), n (%)	14 (74%)	145 (12%)	<0.00001*

Data shown as mean ± SD or n (%). *Fisher exact test was used.
AF = atrial fibrillation or flutter; HCM = hypertrophic cardiomyopathy; NA = not available; NYHA = New York Heart Association; Vo_2 = oxygen consumption.

Illinois). All data are expressed as mean ± SD (range) or frequency (percentage). Differences in continuous variables were assessed using Student *t* test. Pearson chi-square test was used for comparisons between noncontinuous variables, and Fisher exact test when expected frequency was lower than 5. Survival estimates were calculated by the Kaplan-Meier method and log-rank test. Five-year survival values are expressed together with their 95% confidence intervals (CIs) defined as survival ± 1.96 × SE. Statistical significance was defined by a value of $p \leq 0.05$.

Results

Population characteristics. Nineteen patients (1.5%) from the study cohort of 1,226 patients were classified as having "restrictive phenotype." These 19 patients were from 16 unrelated families and included 4 patients with cardiac troponin I mutations who had been previously reported (8). Seven had MLVWT of <13 mm, and 12 patients had MLVWT of 13 to 15 mm. Eleven of the 19 patients had proven familial HCM.

The echocardiographic characteristics of patients at initial evaluation are summarized in Table 1. The average MLVWT was 13 ± 2.7 mm (range 7 to 15 mm). The left atrial diameter was enlarged in all of the patients studied; the mean left atrial size was 53 ± 4.3 mm (range 46 to 60 mm). Left ventricular end-diastolic diameter was either normal or reduced (range 37 to 51 mm), and LV systolic function was preserved in all patients studied (FS: 37 ± 6%). None showed significant mitral regurgitation.

Clinical significance. The clinical characteristics of patients with a "restrictive phenotype" are summarized in Table 2. The patients were age 18 years or more, and the majority (90%) was evaluated because of symptoms or a family history of HCM. At presentation, 12 patients (63%) reported dyspnea (New York Heart Association functional class ≥2), 6 patients had palpitation, and 5 had exertional chest pain. Cardiopulmonary exercise testing confirmed significant limitation; peak VO_2 was 9.0 to 28.8 ml/kg/min (mean: 17.3 ± 6.1 ml/kg/min) (%VO_2: 30% to 87%; mean, 49.3 ± 15.1%).

During a mean follow-up period of 53.7 ± 49.2 months, more patients experienced significant dyspnea (Table 2), and the majority (n = 14, 74%) developed paroxysmal or established atrial fibrillation (Fig. 1). Five patients (26%) experienced a significant embolic stroke, which was the initial presenting feature in 1 patient age 49 years.

Survival. During the follow-up period, 6 (32%) of the "restrictive phenotype" patients (age 35 ± 9 years [21 to 45 years]) died (sudden death in 1 patient, heart failure-related death in 3 patients, and stroke in 1 patient) or underwent cardiac transplantation (n = 1). Left ventricular systolic function and cavity dimensions were normal in all 6 patients at the last evaluation before death. The 5-year event-free survival from any cause of death, cardiac transplantation, or ICD discharge was 56.4% (95% CI 29.7 to 83.2) in

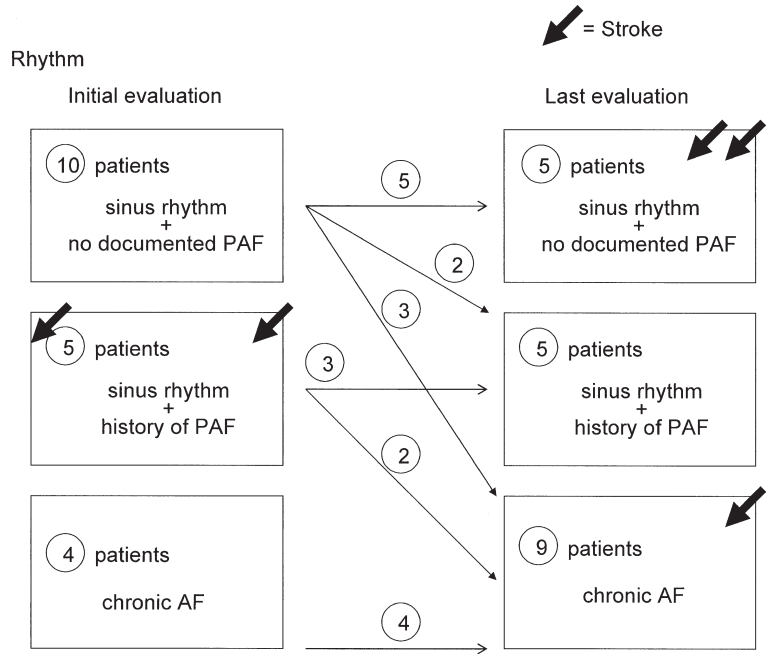

Figure 1 Changes in Rhythm Status in Patients With HCM With Restrictive Phenotype

The figure shows changes in rhythm status from the initial clinical evaluation to the last recent clinical evaluation in 19 patients with hypertrophic cardiomyopathy (HCM) with "restrictive phenotype." AF = atrial fibrillation; PAF = paroxysmal atrial fibrillation.

"restrictive phenotype" patients versus 89.8% (95% CI 87.6 to 92.0) (log-rank p = 0.008) in other HCM patients (n = 1,207) (Fig. 2a). Restrictive phenotype showed a 5.23-fold higher risk for cardiac death or transplantation or ICD discharge (95% CI 2.2 to 12.7, p = 0.0002) when age, LV outflow obstruction, and LVH were included in an event-free survival model. Postmortem examination was performed in 5 of the 6 "restrictive phenotype" patients who died and showed widespread myocardial disarray sufficient to fulfill a histopathological diagnosis of HCM.

Genetic results. Mutation analysis for *MYH7*, *MYBPC3*, *TNNT2*, *TNNI3*, and *TPM1* genes was performed in 15 of the 16 probands with "restrictive phenotype." Sarcomere gene mutations were identified in 8 probands: 4 in *MYH7* and 4 in *TNNI3* (Table 3). Four of the mutations identified were predicted to alter restriction-enzyme sites, and this was confirmed by polymerase chain reaction amplification of the relevant exons, digestion, and size fractionation on a 3% agarose gel. Mutation Arg145Trp in *TNNI3* created an AciI site, mutation Asp190Gly in *TNNI3* abolished a BsrI site, mutation Arg453Cys in *MYH7* created an NlaIII site, and mutation Met493Leu in *MYH7* abolished an NspI site.

The mutations identified in the present study were in functionally important and evolutionarily conserved regions of the genes, and they were present in all affected individuals and absent in at least 170 chromosomes from healthy individuals. One mutation, Met493Leu, in *MYH7* was novel. The proband (Patient #3 in Table 3) was diagnosed as having RCM and died (from heart failure) at the age of 46 years. She did not show significant hypertrophy on echocardiography, and her ECG indicated a low Romhilt-Estes (R-E) score (3 points). Her mother was not affected phenotypically or genotypically. Her father was not evaluated because of death from a malignancy, but he had an otherwise unexplained abnormal 12-lead ECG. The proband's daughter, who carries the identical mutation (Met493Leu), was diagnosed as having HCM with mild LVH (MLVWT: 14 mm) and restrictive physiology. Her ECG showed LVH (R-E score: 6 points). The other mutations detected have been previously reported as disease-causing (8,17).

Seven of the 8 families in whom mutations were identified had a proven family history of 1 or more affected family members with an unequivocal diagnosis of HCM. The other family (Patient #5; Family #H038 in Table 3) had no proven HCM in the family (data not available), but 5 of the relatives had died suddenly before the age of 50 years. Her (Patient #5) autopsy revealed extensive myocardial disarray.

The echocardiographic and Doppler findings in the relatives of the 8 gene-positive families are shown in Table 4. There were 31 gene-positive family members (including patients with the "restrictive phenotype" [n = 9]), and they exhibited variable morphological and hemodynamic phenotypes (no or minimal-to-severe hypertrophy and with or without restrictive filling). One of the relatives

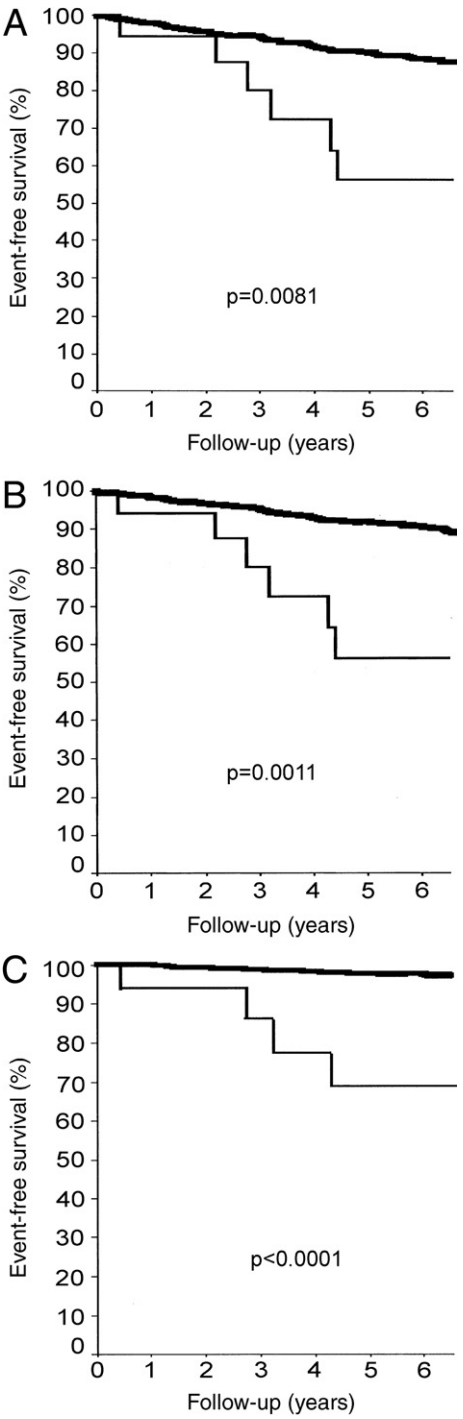

Figure 2 Kaplan-Meier Curves for HCM With Restrictive Phenotype Versus Other HCM

(A) Occurrence of all-cause mortality, cardiac transplantation, or implantable cardioverter-defibrillator discharge during follow-up. Log-rank for trend p = 0.008. **(B)** Occurrence of cardiovascular death, including death from cardiac transplantation and implantable cardioverter-defibrillator discharge, during follow-up. Log-rank for trend p = 0.001. **(C)** Occurrence of heart failure death and cardiac transplantation during follow-up. Log-rank for trend p < 0.0001. **Thin lines** = restrictive phenotype; **thick lines** = other hypertrophic cardiomyopathy (HCM).

Table 3 Results of Genotyping in Probands With "Restrictive Phenotype"

Patient No.	Family No.	Gender	Age at Presentation (yrs)	Sarcomere Gene	Mutation	Proven Familial HCM	LVH on Echocardiography and MLVWT (mm)	Status (Event, Age [yrs])
1	H154	F	34	*MYH7*	Arg453Cys	+	15 mm concentric	Died (stroke, 38)
2	H561	F	28	*MYH7*	Arg453Cys	+	14 mm concentric	Transplant, 31
3	H625	F	45	*MYH7*	Met493Leu	+	11 mm	Died (CHF, 45)
4	H260	M	24	*MYH7*	Val606Met	+	15 mm ASH	Alive
5	H038	F	27	*TNNI3*	Leu144Gln	–	13 mm ASH	Died (CHF, 30)
6	H805	F	67	*TNNI3*	Arg145Trp	+	9 mm	Alive
7	H816	M	70	*TNNI3*	Arg145Trp	+	11 mm	Alive
8	H640	F	25	*TNNI3*	Asp190Gly	+	10 mm	Alive

ASH = asymmetrical septal hypertrophy; CHF = congestive heart failure; LVH = left ventricular hypertrophy; *MYH7* = beta-myosin heavy chain gene; *TNNI3* = cardiac troponin I gene; other abbreviations as in Table 1.

had adverse LV remodeling characterized by cavity enlargement and systolic dysfunction.

Discussion

Hypertrophic cardiomyopathy is a heterogeneous myocardial disorder with a broad spectrum of clinical presentation and morphologic features (1). In this study, we identified a distinct population with "restrictive phenotype" characterized by restrictive filling, minimal or no hypertrophy, and preserved LV systolic function in our HCM cohort, although they were relatively few (1.5% of patients from 2.3% of families). The fact that they had a family history of HCM, typical histology at explant or post mortem, and/or a mutation in beta-myosin heavy chain or cardiac troponin I supports the view that these patients form part of the increasingly diverse spectrum of HCM. Clinical presentation with RCM is uncommon in clinical practice. It is uncertain how often such a presentation is a manifestation of HCM, but our data support such consideration with the inherent clinical implications, perhaps the most important being the need for familial evaluation.

Genotype/phenotype relations. In patients with the "restrictive phenotype," 6 different mutations were identified in 8 probands in *MYH7* and *TNNI3* genes. Five of these mutations have previously been described as disease-causing: 2 in *MYH7* (Arg453Cys, Val606Met) and 3 in *TNNI3* (Leu144Gln, Arg145Trp, Asp190Gly) (8,17). One mutation in *MYH7* (Met493Leu) was novel and localized within an important domain (the relay-helix domain; amino acid residues from numbers 479 to 512) of *MYH7* that has been strictly conserved throughout evolution. To date, only mutations in *TNNI3* have been associated with "restrictive phenotype" in HCM. In this study, we identified for the first time *MYH7* mutations associated with HCM characterized by "restrictive phenotype." The fact that no mutations were found in *MYBPC3*, the most common HCM disease-causing gene, is of interest, particularly as *MYBPC3* mutations appear to cause all of the recognized disease manifestations (18).

How these mutations result in the "restrictive phenotype" has not been systematically evaluated and remains speculative. For *TNNI3* mutations, previous expression studies in HCM revealed increased calcium sensitivity and diminished inhibition of the actomyosin ATPase activity (19,20). The hearts of *TNNI3* transgenic mice showed increased contractility and impaired relaxation (21). Similarly, analyses of muscle mechanics in cardiac myocytes from mice that were engineered to contain a human hypertrophic myosin missense mutation demonstrated increased actin-activated ATPase activity, greater force production, and faster actin-filament sliding (22). The observation of an increase in fiber stiffness under relaxing conditions with a *MYH7* mutation in human slow skeletal muscle has also been reported (23). These findings may influence the development of the "restrictive phenotype." The fact, however, that not all patients from the same family develop the "restrictive phenotype" suggests that other genetic and/or environmental factors are involved and again underscores the genetic/phenotypic heterogeneity of HCM (2).

Table 4 Echocardiographic/Doppler Findings in 31 Family Members Who Carried a Mutation

Restrictive Filling Pattern	MLVWT (≤12 mm)	MLVWT (13 to 15 mm)	MLVWT (16 to 29 mm)	MLVWT (30 mm ≤)
Absent (n = 19)	14 (9*: normal ECG) (5: abnormal ECG)	0	4	1
Present (n = 3 + 9†)	4†	5†	3‡	0

*Of 9 members who were phenotypically negative, 6 were age <16 years and 3 were between 20 and 40 years of age; †these 9 were probands with "restrictive phenotype" in Table 3 and 1 patient (a daughter of Patient #3 in Table 3 as mentioned in the text); ‡1 of them had reduced left ventricular systolic function (fractional shortening = 10%).

ECG = electrocardiogram; MLVWT = maximum left ventricular wall thickness.

Clinical significance of restrictive phenotype. Patients with the "restrictive phenotype" were significantly more limited both subjectively and on cardiopulmonary exercise testing (16). The explanation for the observed exercise impairment relates to the severe diastolic dysfunction. In previous studies, diastolic dysfunction appeared to be one of the most important determinants of exercise capacity in patients with HCM (5–7). These studies have suggested that impairment of diastolic filling with increasing heart rate limits stroke volume augmentation during exercise.

Hypertrophic cardiomyopathy is generally associated with mild disability and normal life expectancy if sudden death can be prevented (24–26). Patients with the "restrictive phenotype," however, had an extremely poor prognosis with an overall survival rate of 56% at 5 years, more closely resembling the poor prognosis of patients with idiopathic RCM (27–29). The main cause of death in "restrictive phenotype" patients was related to heart failure: 42% developed signs of right heart failure, including edema, abdominal discomfort, and ascites. "Restrictive phenotype" patients were also more prone to atrial fibrillation/flutter and stroke, presumably as a consequence of elevated filling pressure and left atrial enlargement (30,31). In general, maintenance of sinus rhythm to avoid loss of atrial contribution to ventricular filling and to reduce embolic risk is desirable, but this may be difficult to achieve in HCM with "restrictive phenotype" given the marked atrial enlargement and rapid progression of right heart failure. The threshold to anticoagulate should, therefore, be low given the significant stroke risk, 26% in this study.

Study limitations. In the present study, we used only mitral flow Doppler indexes to clarify restrictive and nonrestrictive patients because many examinations were performed before tissue Doppler study became available. A more complete analysis of the diastolic function by using tissue Doppler measurements such as diastolic mitral annulus velocities would be desirable in future studies to appropriately assess restrictive physiology.

In this study, although we cannot exclude the possibility that some patients are part of late-stage HCM that leads either to "dilated-hypokinetic" HCM with a dilated LV and systolic impairment, or to "restrictive form" HCM with progressive biatrial dilatation and a restrictive filling pattern of mitral inflow, none of the patients with "restrictive phenotype" was documented in the clinical course of progressive LV remodeling (32–34). Therefore, those patients were considered to present restrictive phenotype resembling RCM as initial manifestation.

We performed genetic screening in 5 sarcomere genes. Other genes, such as cardiac actin, essential myosin light chain, and regulatory myosin light chain, were not analyzed in the "restrictive phenotype" patients. In addition, we did not investigate modifier factors (polymorphisms in the gene encoding renin-angiotensin-aldosterone proteins, for instance) that may contribute to the phenotypic expression.

Conclusions

The "restrictive phenotype" characterized by minimal or no hypertrophy with restrictive filling is part of the clinical spectrum of HCM and is associated with severe limitation, diastolic heart failure, and high rates of atrial fibrillation/flutter and stroke. This phenotype seems to be related to mutations in beta-myosin heavy chain and cardiac troponin I. Prognosis is poor, and patients may ultimately require cardiac transplantation.

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