Interaction of Adverse Disease Related Pathways in Hypertrophic Cardiomyopathy

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Hypertrophic cardiomyopathy (HC) has been characterized as a generally progressive genetic heart disease, creating an ominous perspective for patients and managing cardiologists. We explored the HC disease burden and interaction of adverse clinical pathways to clarify patient expectations over long time periods in the contemporary therapeutic era. We studied 1,000 consecutive HC patients (52 ± 17 years) at Tufts Medical Center, followed 9.3 ± 8 years from diagnosis, employing a novel disease pathway model: 46% experienced a benign course free of adverse pathways, but 42% of patients progressed along 1 major pathway, most commonly refractory heart failure to New York Heart Association class III or IV requiring surgical myectomy (or alcohol ablation) or heart transplant; repetitive or permanent atrial fibrillation; and least commonly arrhythmic sudden death events. Eleven percent experienced 2 of these therapeutic end points at different times in their clinical course, most frequently the combination of advanced heart failure and atrial fibrillation, whereas only 1% incurred all 3 pathways. Freedom of progression from 1 to 2 disease pathways, or from 2 to 3 was 80% and 93% at 5 years, respectively. Annual HC-related mortality did not differ according to the number of pathways: 1 (0.8%), 2 (0.8%), or 3 (2.4%) (p = 0.56), and 93% of patients were in New York Heart Association classes I or II at follow-up. In conclusion, it is uncommon for HC patients to experience multiple adverse (but treatable) disease pathways, underscoring the principle that HC is not a uniformly progressive disease. These observations provide a measure of clarity and/or reassurance to patients regarding the true long-term disease burden of HC. **(Am J Cardiol 2017;120:2256–2264)**

Hypertrophic cardiomyopathy (HC) is a relatively common genetic heart disease for which patients can be encumbered by a number of adverse clinical outcomes,[1–5] including sudden death (SD),[6–10] heart failure (HF) refractory to maximum medical management with or without left ventricular (LV) outflow tract obstruction,[11–18] or symptomatic atrial fibrillation (AF).[19–24] Due to this heterogeneous clinical profile, HC patients may experience substantial uncertainty regarding their prognosis and lifestyle, including the possibility of incurring multiple adverse disease-related events over long periods of time requiring major treatment interventions, and with certain expectations for survival and acceptable quality of life.[1–5,25–27] In this analysis we have assessed a large cohort of 1,000 consecutive HC patients to define the frequency and interaction of adverse disease pathways, and clarify the long-term burden of HC.

Methods

Databases from the Hypertrophic Cardiomyopathy Institute at Tufts Medical Center identified 1,021 consecutive patients, ≥10 years of age at diagnosis, from 2003 to 2013 inclusive. Patients were referred for targeted subspecialty evaluations, including risk stratification and treatment options, or to establish definitive diagnosis of HC; no study patient was identified from systematic pedigree studies, or other broad-based screening initiatives.

Most recent clinical status was established by hospital visit or telephone contact (or by Social Security death index). Twenty-one patients were lost to follow-up and therefore the final study population comprised 1,000 patients for whom complete and detailed clinical records were available at follow-up. Duration of follow-up was 9.3 ± 8 years (median 6.6 years) from initial HC diagnosis by imaging the disease phenotype to most recent contact (or death). The Tufts HC Institute practice consists of routine clinical follow-up on an annual basis, with history and physical examination, 12-lead electrocardiogram, echocardiography and cardiovascular magnetic resonance (CMR), 24- to 48-hour ambulatory (Holter) ECG, and selective stress (exercise) echocardiography.

At first visit, HC diagnosis was based on echocardiographic and/or CMR demonstration of a hypertrophied and nondilated left ventricle with wall thickness ≥13 mm, in the absence of another cardiac or systemic disease capable of producing a similar magnitude of hypertrophy.[1–4] Patients with known phenocopies of HC (e.g., Fabry disease, Danon disease, or

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amyloidosis) were excluded. This study was reviewed and approved by Institutional Review Boards at Tufts Medical Center.

Transthoracic echocardiographic studies were performed in standard fashion. LV wall thickness was measured as the maximal end-diastolic dimension within the chamber (usually ventricular septum). Continuous-wave Doppler was used to estimate peak instantaneous LV outflow gradient. Outflow obstruction was defined as gradient ≥30 mmHg at rest and with exercise on stress echocardiography, and the nonobstructive state as <30 mmHg at rest or with exercise.[18,28]

CMR studies were performed in 403 patients with 1.5-T clinical scanner with cine sequences in standard views with full LV coverage. Late gadolinium enhancement images were acquired 10 to 15 minutes after intravenous administration of 0.2 mmol/kg gadolinium-diethylene triamine pentaacetic acid, using breath-held segmented inversion-recovery sequences. Late gadolinium enhancement quantification was performed by manually adjusting gray scale threshold to visually define areas of late gadolinium enhancement, which were summed and expressed as a proportion of total LV myocardium as previously reported.[29]

Single- or dual-chamber implantable cardioverter defibrillators (ICDs) capable of antitachycardia and antibradycardia pacing were implanted for primary (n = 324) or secondary (n = 17) prevention. Risk stratification and ICD decision making was according to US/Canada (American College of Cardiology Foundation/American Heart Association) guidelines. Expert electrophysiologists analyzed and adjudicated stored intracardiac electrocardiograms to define arrhythmias responsible for appropriate defibrillator interventions, according to previous definitions.[7,10]

Heart rate cutoff criteria for detecting of ventricular tachyarrhythmias were programmed, and antitachycardia pacing was activated at the discretion of the managing electrophysiologist. Defibrillator discharges were considered appropriate when triggered by ventricular fibrillation or rapid ventricular tachycardia (rate >200 per minute) documented by stored electrographic or cycle length data. Interventions were considered inappropriate when triggered by heart rate exceeding the programmed threshold, such as with either supraventricular arrhythmias or sinus tachycardia.

This study is structured to assess the natural history of HC patients relative to 3 hallmarks of disease progression: (1) SD events, including appropriate ICD interventions for ventricular fibrillation or rapid ventricular tachycardia documented by device interrogation, or survival from resuscitated out-of-hospital cardiac arrest; (2) progression of HF symptoms, as assessed in accord with personal history, to New York Heart Association (NYHA) functional class III or IV, refractory to maximum medical management, and due either to outflow obstruction, or alternatively in the absence of outflow obstruction, that is, end-stage with low or preserved ejection fraction; (3) AF, that is, permanent or persistent, or repetitive symptomatic and clinically recognized paroxysmal episodes (n >2), requiring consideration for therapeutic interventions to restore sinus rhythm.[19–24] Asymptomatic clinically silent episodes of paroxysmal AF identified only by nonsystematic monitoring studies were not included.[30]

Data are mean ± standard deviations for continuous variables and proportions for categorical variables; for continuous variables with non-normal distributions, data are presented as median (25th, 75th percentiles). Student's *t* test, Wilcoxon rank-sum tests, and analysis of variance tests were used to assess statistical significance of continuous variables, whereas chi-square or Fisher's exact test were used for categorical variables.

Event-free survival rates at 5 and 10 years for specific disease pathways were estimated by Kaplan-Meier method. Statistical calculations were performed using Stata version 11.2 software and SAS version 9.3. Selected clinical data reported here also appear in other studies.[25–27]

Results

In an overall analysis of the 1,000 study patients, ages were 43 ± 18 years at HC diagnosis, 48 ± 17 years at initial visit, and 52 ± 17 years at most recent evaluation (or death); 24% were 60 to 69, and 13% were ≥70. Maximal LV wall thickness was 20 ± 5 mm (Table 1). Initially, most patients (70%) were asymptomatic or mildly symptomatic in NYHA classes I and II.

Of the overall 1,000 patients, 461 (46%) did not evolve along any of the 3 adverse pathways over follow-up (Figure 1; Table 1). Of these 461 patients, 98% have survived with a largely benign or stable course to age 49 ± 17 years in NYHA class I (72%) and class II (28%) (Table 2).

The remaining 539 patients (54%) evolved along 1 or more predefined adverse disease pathways (Figure 2). Most common of these was drug-refractory progressive HF (NYHA class III or IV) in 429 patients, including 387 with outflow obstruction (Table 1).

The predefined AF end point was reached in 172 patients, and the least common pathway was arrhythmic SD events occurring in 57 patients (6%), including 8 with SD, 32 with appropriate ICD interventions, and 17 with resuscitated cardiac arrest (including 7 with subsequent secondary prevention ICD discharges).

Of the 1,000 patients, 427 (42%) evolved to only 1 adverse pathway at 49 ± 17 years of age (Figure 3). The most common clinical course involved drug-refractory progressive HF (NYHA class III or IV) occurring in 319, leading to myectomy (or alcohol ablation) in 260 or heart transplant in 7.

Sixty-nine 1-pathway patients experienced symptomatic paroxysmal AF or permanent AF. The remaining 39 one-pathway patients (9%) had ventricular arrhythmic events: 6 SDs, 19 ICD interventions, and 14 resuscitated cardiac arrests. Of the 427 one-adverse pathway patients, 92% have survived, including 87% in classes I or II at follow-up (Table 2).

Evolution along 2 adverse pathways occurred in 105 patients (10.5%) (Figures 3 and 4). Time from initial adverse pathway to onset of second pathway was 3.5 years on average, but highly variable (i.e., 2 months to 26 years).

Most frequent combination was AF and progressive HF occurring in 90%. HF developed before AF in 35 patients by 3.8 ± 5.0 years, whereas AF occurred first in 59 patients by 3.5 ± 3.8 years. Nine patients incurred both advanced HF and SD events, with HF preceding SD events in 6 patients and SD events occurring first in 3 patients. Of the 105 patients with 2 adverse pathways, 90% have survived to 58 ± 13 years, 80% in NYHA classes I and II.

All 3 adverse pathways occurred in 7 study patients (1%). Time from HC diagnosis to onset of first pathway was 5.9 ± 5.0