Low Risk of Hypertrophic Cardiomyopathy With Contemporary Management Strategies Implemented in Non-Referral Regional Community-Based Practices

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Major advances in diagnosis and treatment have emerged for hypertrophic cardiomyopathy (HCM), largely in major tertiary referral centers dedicated to this disease. Whether these therapeutic benefits are confined to patients in such highly selected cohorts, or can be implemented effectively in independent regional or community-based populations is not generally appreciated. We assessed management and clinical outcomes in a non-referral HCM center (n = 214 patients) in Eastern Pennsylvania. Over a 6.0 ± 3.2-year follow-up, the HCM-related mortality rate was 0.1% per year attributed to a single disease-related death, in a 49-year-old man with end-stage heart failure, ineligible for heart transplant. Fifteen patients (7%) with prophylactically placed implantable cardioverter-defibrillators (ICDs) experienced appropriate therapy terminating life-threatening ventricular tachyarrhythmias. In 23 other patients (11%; 5%/year), heart failure due to left ventricular outflow obstruction was reversed by surgical septal myectomy (n = 20) or percutaneous alcohol septal ablation (n = 3). This regional HCM cohort was similar to a comparison tertiary center referral population in terms of HCM-mortality: 0.1%/year vs 0.3%/year (p = 0.3) and ICD therapy (31% vs 16% of primary prevention implants), although more frequently with uncomplicated benign clinical course (62% vs 46%; p <0.01). In conclusion, effective contemporary HCM management strategies and outcomes in referral-based HCM centers can be successfully replicated in regional and/or non-referral settings. Therefore, HCM is now a highly treatable disease compatible with normal longevity when assessed in a variety of clinical venues not limited to tertiary centers. © 2020 Published by Elsevier Inc. (Am J Cardiol 2021;142:130−135)

Hypertrophic cardiomyopathy (HCM) is a relatively common inherited heart disease that has achieved visibility in cardiovascular medicine largely through reports from tertiary referral centers.[1−3] It is in such institutions where the highest risk HCM patients have traditionally clustered, with the greatest access to effective treatment strategies and the potential to reduce mortality and morbidity. This recognition raises the question of whether lessons learned in HCM tertiary referral centers can be translated to (and implemented in) non-tertiary-based regional or community-based patient populations.[4] To study this issue, we analyzed the multidisciplinary management and outcome of HCM in a novel non-referral based regional cohort.

Methods

Over the last 10 years (since 2010), a regional HCM center has diagnosed and managed HCM patients in the Lehigh Valley region of Eastern Pennsylvania. This HCM program is part of the St. Luke's University Health Network of clinics and hospitals that serve communities in 7 counties of Eastern Pennsylvania, principally Lehigh and Northampton (population 675,000) and is a regional campus for the Lewis Katz School of Medicine of the Temple University in Philadelphia (Temple-St. Luke's School of Medicine). The program comprises 11 local and one central hospital in Bethlehem and 14 out-patient cardiac clinics, with 41 network-employed cardiologists including electrophysiologists and cardiac surgeons.

The present study cohort is comprised of 214 consecutive HCM patients followed for 6.0 ± 3.2 years (range to 1 to 9). Excluded patients were those with HCM phenocopies (LAMP2 cardiomyopathy, amyloidosis, and Fabry disease), combined abnormalities (e.g., subvalvular membrane), as well as genotype positive-phenotype negative family members. Management and outcome metrics were compared with that in a consecutive tertiary HCM center cohort (Tufts Medical Center) evaluated from 2001 to 2017.

Maximum left ventricular (LV) wall thickness was taken at any site in the LV chamber at end-diastole. Peak instantaneous LV outflow tract gradient was estimated at rest with continuous wave Doppler interrogation. Patients with gradients <50 mm Hg at rest had provocation using symptom-limited exercise (stress) testing with echocardiography on a standard Bruce protocol, as previously described.

Cardiovascular magnetic resonance (CMR) studies were performed in 80 patients using a 1.5-T clinical scanner with cine sequences in standard views and full LV coverage. Areas of late gadolinium enhancement were quantified by manually adjusting the gray scale threshold, and expressed as a proportion of total LV myocardium.

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See page 134 for disclosure information.

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Results

Baseline clinical characteristics in the 214 study patients are shown in Table 1. At initial evaluation (study entry), patients were 50 ± 14 years of age: 25 were <30 years (12%) and 65 were >60 years (30%); 119 patients (56%) were men. At last evaluation after follow-up of 6.0 ± 2 years, ages were 58 ± 17 years (range 11 to 97). Maximum LV wall thickness by echocardiography and/or CMR was 18 ± 5 mm (range 13 to 33), including 3 patients (2%) ≥ 30 mm.

At initial evaluation, 167 patients (78%) had no or only mild functional limitation (New York Heart Association [NYHA] classes I or II) while the other 47 patients (22%) had advanced NYHA class III or IV drug-refractory heart failure symptoms. At most recent evaluation, the majority of patients were in NYHA classes I or II (n = 187; 87%). The other 27 patients (13%) had marked class III heart failure symptoms, refractory to β-blockers and/or verapamil.

LV outflow gradients ≥ 30 mm Hg were present at rest in 65 of 214 patients (30%) due to typical dynamic mitral valve systolic anterior motion with septal contact, or with physiologic exercise provocation (by stress echocardiography), (n = 45). The remaining patients were nonobstructive with mild (< 30 mm Hg) or no gradient at rest and with exercise.

Genetic testing assessing in 8 most common HCM myofilament genes was performed selectively in probands with positive HCM family history. In 30 of the 48 probands, a pathogenic (disease-causing) sarcomere mutation was identified (MYBPC=21; MYH7=6; TNNI=3). Testing in the remaining 18 patients yielded variants of unknown significance (11; 23%) or absence of sarcomere mutations (n = 7; 14%).

Of the study group, 48 patients were judged to be at increased risk for sudden death based on identification of ≥ 1 risk markers considered as major within the patient's clinical profile, and implanted with ICDs for primary prevention.[5] Of these, 15 (31%) have experienced appropriate device therapy 3.3 ± 3.1 years after implant (5%/year) for ventricular fibrillation and/or rapid sustained ventricular tachycardia restoring sinus rhythm, representing 7% of the cohort; multiple device therapies occurred in 6 patients. The 15 patients with ICD interventions had either 1 (n = 4), 2 (n = 9), or ≥ 3 (n = 2) risk markers, the most common of which were: family history of HCM-sudden death and nonsustained ventricular tachycardia on ambulatory monitoring.

Twenty-nine patients with outflow obstruction, (69 ± 26 mm Hg at rest; 87 ± 38 mm Hg physiologically provoked) developed progressive symptoms to NYHA class III or IV; 20 of these underwent surgical septal myectomy,[5-7] including 3 with mitral valve repair and 2 with concomitant mitral valve replacement.[5] Resting outflow gradients decreased from 78 ± 21 mm Hg preoperatively to 17 ± 9 mm Hg after operation. Over 4.3 ± 2.5 years of follow-up each of these patients have improved by ≥ 1 NYHA functional class (NYHA I in 17 or II in 3). Three other patients declined surgery and underwent percutaneous alcohol septal ablation; gradients at rest were reduced from 66 ± 25 to 19 ± 10 mm Hg with each returned to NYHA class I or II. Of the combined 23 patients with invasive interventions to relieve outflow obstruction, there were no operative or procedural (30 day) deaths.

Eight symptomatic patients with systolic dysfunction (ejection fraction 25% to 50%, mean 40 ± 11%), were judged to be in the end-stage of HCM representing 3.7% of the cohort. Seven patients are presently treated medically with class II symptoms and one is listed for heart transplantation.

Thirty-six of 214 patients (17%) have experienced atrial fibrillation,[8] permanent in 5, and/or with paroxysmal episodes in 31, including 11 who underwent radiofrequency catheter-ablation. Of those 11 patients, 5 have maintained sinus rhythm for 456 ± 447 days. There have been 7 nonfatal embolic strokes, including 4 patients without anticoagulation prophylaxis (i.e., noncompliance in 1, atrial fibrillation on initial clinical presentation in 2, and during cardiac catheterization in one). Of the 7 stroke patients, none have incurred significant permanent neurologic disability.

Overall, clinical outcome was considered benign and stable in 132 patients (62%), defined as persistent NYHA class I or II symptoms without major disease-related events or complications. In 38 patients, potentially lethal complications were aborted by major interventions[2]: ventricular tachyarrhythmias terminated by primary prevention ICDs (n = 15); reversal of progressive heart failure due to LV outflow tract obstruction with myectomy and/or alcohol septal ablation (n = 23).[2]

Notably, among the 214 study patients, only one has died of causes directly related to HCM, a 49-year-old man with end-stage heart failure, systolic dysfunction (EF=30%), and dilated LV who also had idiopathic refractory thrombocytopenia that excluded him from heart transplant consideration. There have been 18 deaths due to non-HCM related causes, including 5 in patients over age 80 (range to 89), most commonly due to cancer (n = 4); pneumonia (n = 4); motor vehicle accidents (n = 2); coronary artery disease (n = 1) and chronic co-morbid conditions (i.e., diabetes, renal disease, scleroderma, giant cell arthritis, stroke unrelated to HCM).

The referral and non-referral cohorts were similar in most demographic respects, including age at first evaluation, LV wall thickness and LV outflow tract gradient, nonsustained ventricular tachycardia on ambulatory electrocardiogram, NYHA class at initial evaluation, and genetic markers (Table 1).

Notably, when compared with the tertiary HCM center referral cohort, the regional community study population demonstrated a similar low HCM-related mortality, 0.1% per year versus 0.3% per year (p = 0.3) reflecting in part the aborted sudden deaths with primary prevention ICDs (31% of implants vs 16% in tertiary patients; p = 0.03), and with a similar proportion of patients receiving ICDs (22% vs 25%; p = 0.4).

Compared with the tertiary referral patients, the regional cohort had a smaller proportion of severely symptomatic (NYHA class III or IV) drug refractory patients at initial evaluation (22% vs 34%; p = 0.03), many of whom became candidates for surgical myectomy (or alternatively alcohol ablation). Regional patients were more likely to experience benign and largely uncomplicated clinical course (62% vs 46%; p < 0.01).

Table 1
Demographics and clinical features of HCM patients in a regional community practice compared with HCM patients in a tertiary referral center

Parameter	Regional Patients (n=214)	Tertiary Center Patients (n=2,123)	p value
Males	119 (56%)	1329 (63%)	0.04
Age at diagnosis (years)	49 ± 13	46 ± 18	0.02
Age at first visit (years)	50 ± 14	51 ± 17	0.04
Age at last evaluation (years)	58 ± 17	56 ± 16	0.08
Family history of HCM	47 (22%)	510 (24%)	0.50
Family history − HCM sudden death	22 (7%)	226 (11%)	0.97
Syncope, n (%)	29 (10%)	258 (12%)	0.85
NSVT on ambulatory monitoring	21 (10%)	320 (15%)	0.04
Maximum LV wall thickness (mm)	18 ± 5	19 ± 4	<0.01
No. patients LV ≥ 30mm	3 (2%)	127 (6%)	<0.01
No. LV apical aneurysm	4 (2%)	73 (3%)	0.22
Ejection fraction, (%)	67 ± 9	64 ± 6	0.03
Left atrial dimension (mm)	40 ± 6	41 ± 7	0.04
Peak LV outflow gradient, ≥ 30 mmHg (rest)	65 (30%)	765 (36%)	0.10
LVEDD (mm)	41 ± 9	42 ± 7	0.05
Contrast-CMR			
No. CMR studies	103	1128	
No. with LGE	61 (59%)	639 (57%)	0.80
% LGE (in patients with LGE)	4.6 ± 5.1	5.8 ± 5.7	<0.01
No. LGE ≥ 15% of LV	8 (7.7%)	58 (5%)	0.26
NYHA-functional class, initial evaluation			
I	92 (43%)	832 (39%)	0.30
II	75 (35%)	674 (32%)	0.32
III/IV	47 (22%)	618 (29%)	0.03
No. with atrial fibrillation	36 (17%)	545 (26%)	<0.01
No. septal myectomy	20 (9.3%)	630* (30%)	<0.01
Operative mortality	0	5 (0.8%)	0.69
Post-operative NYHA class I/II	20 (100%)	598 (96%)	0.36
No. alcohol septal ablations	3 (1.4%)	147* (7%)	<0.01
No. heart transplants	0	31 (1.5%)	0.07
Primary prevention ICD, (%)	48 (22%)	527 (25%)	0.44
Age at ICD implantation (years)	44 ± 13	42 ± 16	0.08
Primary prevention ICD therapy, n (% of implants)	15 (31%)	82 (16%)	<0.01
Resuscitated cardiac arrest	3 (1.4%)	36 (1.7%)	0.88
ICD complications	10 (21%)	85 (16%)	0.40
Inappropriate shocks	9	61	
Device infection	1	14	
Lead fracture	2	21	
ICD complication rate (% / y)	2.4%	2.1%	
Drug therapy (number patients)			
Beta-blockers	187 (87%)	1644 (77%)	<0.01
Calcium antagonists	129 (60%)	875 (41%)	<0.01
Disopyramide	14 (7%)	193 (9%)	0.21
ACE/ARB	48 (22%)	620 (29%)	0.04
Amiodarone	8 (4%)	282 (13%)	<0.01
Genetic Testing	48	351	
MYBPC3	21	88	
MYH7	6	57	
TNNT2	0	12	
MYL2, MYL3	0	4	
TPM1	0	4	
TNNI	3	8	
MYBPC3 + TNNI	0	2	
MYH7 + MYBPC3	0	3	
NYHA-functional class, last evaluation			
I	88 (41%)	1039 (52%)	0.002
II	99 (46%)	845 (43%)	0.31
III/IV	27 (13%)	104 (5%)	0.0001
All Deaths	18 (8%)	135 (6%)	0.40
Age at death	68 ± 15	67 ± 15	
Non-cardiac death	16 (7%)	101 (5%)	0.12

(*continued*)

Table 1 (***Continued***)

Parameter	Regional Patients (n=214)	Tertiary Center Patients (n=2,123)	p value
Cardiac- non-HCM	1 (0.5%)	7 (1%)	
Unknown	1 (0.5%)	6 (0.3%)	
HCM-related death	1 (0.5%)	28 (1.3%)	0.29
Sudden	0	5	
Heart failure	1	12	
Post-transplant	0	3	
Post-operative	0	5	
Embolic stroke death	0	3	
Age at HCM-death	49	56	
HCMM-mortality rate, %/y	0.1	0.3	0.3

ACE/ARB = angiotensin converting enzyme inhibitors or angiotensin receptor blocker; CMR = cardiovascular magnetic resonance; EF = ejection fraction; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LVED = left ventricular end-diastolic dimension; LV = left ventricular; NYHA = New York Heart Association; SD = sudden death; y = years.

* Includes 21 patients with unsuccessful alcohol septal ablation prior to myectomy. 29 prior to initial visit. In surviving patients. Includes 1 patient who underwent mitral value replacement after myectomy.

Discussion

Highly specialized national referral centers dedicated to HCM have reported a reduction in disease-related mortality and morbidity attributable to the introduction of contemporary treatment advances to this patient population.[1–3] However, because most HCM patients are initially identified and frequently managed in non-referral community-based cardiovascular settings outside of tertiary centers, we considered here whether currently available treatment paradigms can also be effectively implemented in regional or local practices. In this regard, we have accessed an active nontertiary referral HCM program regionally based in Bethlehem, Pennsylvania to assess disease course, management and outcome encountered in such a clinical environment.

This novel analysis demonstrated several principles related to the HCM disease spectrum. Most importantly, management strategies propagated in traditional tertiary centers[1,2,5,7,9,10] can be effectively translated with favorable results to patients in regional and/or local settings that exhibit similar demographics (Figure 1), and even in community private practice settings.[4] Indeed, the regional patient cohort in

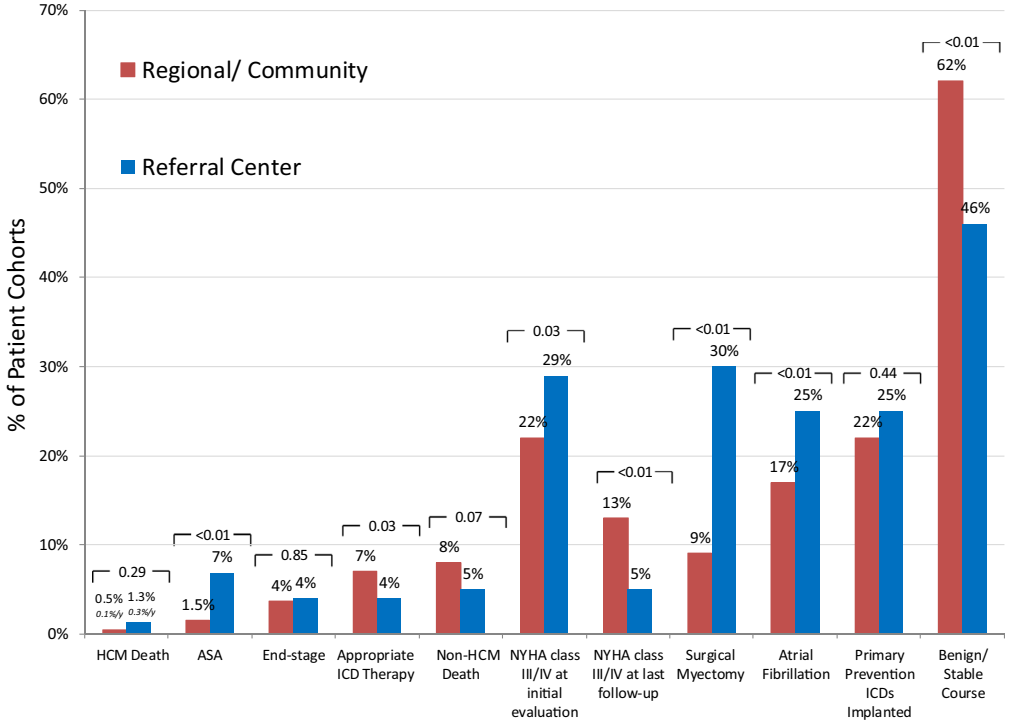

Figure 1. Implementation of contemporary management strategies in a regional hypertrophic cardiomyopathy program compared with a tertiary referral-based center. ASA = alcohol septal ablation; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association.

Eastern Pennsylvania reported here was similar to that of a representative tertiary referral cohort analyzed for comparison with regard to demographics, morphology, management initiatives and decision-making, as well as clinical outcome.[1] These observations stand in stark contrast to a previous era for HCM when tertiary centers (such as NIH) reported the skewed referral of highly selected patients with particularly advanced disease.[11,12]

Of particular note, HCM-related mortality in the regional cohort proved to be exceedingly uncommon (0.1%/year), given that only one patient in the cohort has died of causes related to HCM i.e., due to nonobstructive end-stage heart failure and ineligible for heart transplant due to significant co-morbidity. This low mortality rate is consistent with that reported from tertiary center populations in which HCM-related deaths are also largely confined to patients with advanced or end-stage heart failure in the absence of outflow obstruction.[12]

Furthermore, using the enhanced ACC and/or AHA risk stratification algorithm with ≥ 1 patient markers judged major within the patient's clinical profile (including those CMR-related), the primary prevention ICD initiative for HCM patients proved to be highly effective (5%/year with appropriate therapy). Therefore, ICDs were an important determinant of the low mortality rate cited here[1,2,13] by effectively terminating potentially lethal ventricular tachyarrhythmias in 15 patients who constituted about 30% of those with prophylactically implanted devices, notably a similar if not higher rate than in the present comparison and other tertiary center cohorts.[14–17]

The regional cohort comprised a significant proportion of drug-refractory patients with advanced NYHA class III and/or IV heart failure symptoms, due predominantly to LV outflow obstruction. Twenty of these 29 patients have undergone surgical myectomy with favorable results similar to that in the tertiary referral center, i.e., very low operative mortality with the vast majority of patients (>90%) experiencing postoperative symptom relief to NYHA classes I or II.[5–7]

In conclusion, in a regional HCM cohort with contemporary treatment innovations, there was successful termination of arrhythmic sudden death events and invasive reversal of heart failure without procedural mortality. These observations in a non-referral community setting proved not dissimilar to those reported from a comparison tertiary HCM center. This extends the principle that with implementation of contemporary strategies, HCM is now a treatable inherited heart disease with the expectation for good quality of life and a lower mortality risk than is evident with other disease-related risks of living.[18]

Authors Contribution

Jamshid Shirani: Conceptualization, Methodology, Data Curation, Writing-Review and Editing; Rasha Aurshiya: Data Curation, Formal analysis, Writing-Review and Editing; Abdelsalam Elshaikh: Data Curation, Formal analysis, Writing-Review and Editing; Stephen A. Olenchock: Writing-Review and Editing, Supervision; Ethan J. Rowin: Conceptualization, Methodology, Data Curation, Writing-Review and Editing, Supervision; Martin S. Maron: Conceptualization, Methodology, Data Curation, Writing-Review and Editing, Supervision; Barry J. Maron: Conceptualization, Methodology, Data Curation, Writing-Original draft, Supervision.

Disclosures

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 study.

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