Comparison of Outcomes in Patients With Nonobstructive, Labile-Obstructive, and Chronically Obstructive Hypertrophic Cardiomyopathy

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Patients with nonobstructive hypertrophic cardiomyopathy (HC) are considered low risk, generally not requiring aggressive intervention. However, nonobstructive and labile-obstructive HC have been traditionally classified together, and it is unknown if these 2 subgroups have distinct risk profiles. We compared cardiovascular outcomes in 293 patients HC (96 nonobstructive, 114 labile-obstructive, and 83 obstructive) referred for exercise echocardiography and magnetic resonance imaging and followed for 3.3 ± 3.6 years. A subgroup (34 nonobstructive, 28 labile-obstructive, 21 obstructive) underwent positron emission tomography. The mean number of sudden cardiac death risk factors was similar among groups (nonobstructive: 1.4 vs labile-obstructive: 1.2 vs obstructive: 1.4 risk factors, p = 0.2). Prevalence of late gadolinium enhancement (LGE) was similar across groups but more non-obstructive patients had late gadolinium enhancement ≥20% of myocardial mass (23 [30%] vs 19 [18%] labile-obstructive and 8 [11%] obstructive, p = 0.01]. Fewer labile-obstructive patients had regional positron emission tomography perfusion abnormalities (12 [46%] vs nonobstructive 30 [81%] and obstructive 17 [85%], p = 0.003]. During follow-up, 60 events were recorded (36 ventricular tachycardia/ventricular fibrillation, including 30 defibrillator discharges, 12 heart failure worsening, and 2 deaths). Nonobstructive patients were at greater risk of VT/VF at follow-up, compared to labile obstructive (hazed ratio 0.18, 95% confidence interval 0.04 to 0.84, p = 0.03) and the risk persisted after adjusting for age, gender, syncope, family history of sudden cardiac death, abnormal blood pressure response, and septum ≥3 cm (p = 0.04). Appropriate defibrillator discharges were more frequent in nonobstructive (8 [18%]) compared to labile-obstructive (0 [0%], p = 0.02) patients. In conclusion, nonobstructive hemodynamics is associated with more pronounced fibrosis and ischemia than labile-obstructive and is an independent predictor of VT/VF in HC. **(Am J Cardiol 2015;■:■−■)**

Novel imaging technologies have indicated that characteristics unrelated to outflow hemodynamics but related to the primary myopathy, such as fibrosis by imaging,[1] microvascular ischemia,[2,3] and abnormal myocardial mechanics,[4,5] are highly prevalent in hypertrophic cardiomyopathy (HC) and may be important arbiters of outcomes.[1,6,7] Therefore, nonobstructive hemodynamics alone may not always confer low risk, a viewpoint corroborated by several anecdotal examples in our large-volume practice. Moreover, previously published outcome studies did not separate nonobstructive (resting and provoked gradients <30 mm Hg) and labile-obstructive (resting <30 mm Hg; provoked ≥30 mm Hg) variants,[8−10] as is the current clinical practice.[11] Therefore, it is additionally unclear if there are differences in outcomes between nonobstructive versus labile-obstructive HC phenotypes not evident in existing published reports since both these groups were combined.

Methods

This study was approved by the institutional review board. A total of 344 patients were recruited at their first visit to the Johns Hopkins Hypertrophic Cardiomyopathy Center from 2005 to 2013 if they fulfilled previously used diagnostic criteria for HC, which primarily was a maximal septal wall thickness ≥15 mm in the absence of other cardiac or systemic disease that may produce a similar degree of left ventricular (LV) hypertrophy,[8,11,12] and 293 of them were followed for a mean of 3.3 ± 3.6 years. Patients with a previous myectomy or alcohol septal ablation were excluded. Clinical information was collected as previously

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See page 6 for disclosure information.

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Table 1
Baseline characteristics

Variable		Non-Obstructive (n=96)	Labile-Obstructive (n=114)	Obstructive (n=83)	Total (n=293)	p-value
Length of follow-up (years)		3.5±3.8	3.2±3.5	2.8±3.2	3.3±3.6	0.5
Age (years)		49±15	50±15	55±13	51±15	0.01
Male		60 (63%)	83 (73%)	51 (61%)	194 (66%)	0.2
Body Mass Index (kg/m^2)		29.4±5.7	29.7±5.3	30.4±6.0	29.8±5.7	0.5
NYHA	I	64 (67%)	71 (62%)	30 (36%)	165 (56%)	<0.001
	II	24 (25%)	24 (21%)	37 (45%)	85 (29%)	
	III	8 (8%)	19 (17%)	16 (19%)	43 (15%)	
Angina pectoris		33 (34%)	46 (40%)	37 (45%)	116 (40%)	0.4
Syncope		17 (18%)	25 (22%)	14 (17%)	56 (19%)	0.6
Ventricular tachycardia/fibrillation		10 (10%)	0 (0%)	1 (1%)	11 (4%)	<0.001
Non-sustained ventricular tachycardia		18 (19%)	9 (8%)	8 (10%)	35 (12%)	0.047
Atrial Fibrillation		17 (18%)	9 (8%)	8 (10%)	34 (12%)	0.08
Implantable Cardioverter Defibrillator		18 (19%)	6 (5%)	9 (11%)	33 (11%)	0.009
Family History						
Hypertrophic Cardiomyopathy		29 (31%)	16 (15%)	10 (12%)	55 (19%)	0.003
Sudden cardiac death		26 (27%)	28 (26%)	19 (23%)	73 (25%)	0.8
Sudden cardiac death risk factors		1.4±1.1	1.2±1.0	1.4±1.0	1.3±1.0	0.2
Medications						
β-blocker		68 (71%)	77 (68%)	67 (81%)	212 (73%)	0.1
Disopyramide		0 (0%)	6 (5%)	5 (6%)	11 (4%)	0.06
Ca-blocker		13 (14%)	28 (25%)	25 (30%)	66 (23%)	0.02

described.[13] We compared clinical features and outcomes within the 3 HC subgroups.

Sustained ventricular tachycardia (VT), ventricular fibrillation (VF), appropriate implantable cardioverter defibrillator (ICD) discharge, heart failure worsening (defined as New York Heart Association (NYHA) class worsening to class III or IV), and death were recorded by reviewing Holter and exercise electrocardiographic tracings, ICD interrogation reports, and clinical visit notes. Appropriate ICD discharges were defined as documented VT or VF events at heart rate ≥180betas/min.[14,15] Sudden cardiac death (SCD) risk was assessed by noting nonsustained ventricular tachycardia (NSVT), unexplained syncope of non-neurocardiogenic origin, previous VT/VF, family history of SCD, septum ≥3 cm, and abnormal blood pressure response.[11]

Echocardiography was performed using a GE Vivid 7 ultrasound machine (GE Ultrasound, Milwaukee, Wisconsin) using a standard clinical protocol. Conventional measurements were performed as previously published.[16,17] Systolic anterior movement of the mitral valve was defined as absent, incomplete (no contact with the septum), and complete (contact between leaflet and septum).[18] LV outflow tract (LVOT) gradients were measured before and immediately after a symptom-limited exercise test,[19,20] and patients were classified into nonobstructive (<30 mm Hg at rest and exercise), labile-obstructive (<30 mm Hg at rest and ≥30 mm Hg with exercise), and obstructive (≥30 mm Hg at rest).[11]

Cardiac magnetic resonance imaging was performed on a 1.5T system (MAGNETOM Avanto; Siemens Healthcare, Erlangen, Germany), as described previously,[21] with contrast, gadopentetate dimeglumine at 0.2 mmol/kg (Magnevist; Bayer Schering, Berlin, Germany). Late gadolinium enhancement (LGE) images were assessed in short-axis view with validated software (QMASS 7.4; Medis, Leiden, The Netherlands) by an experienced reader (C.C.V). Endocardial and epicardial borders were manually traced in each slice, and the myocardium was divided into 16 segments starting from the anterior insertion point of the right ventricle. A region of interest was placed in an area of normal appearing nulled myocardium, typically the basal lateral wall. Pixels with signal intensity >6 standard deviations greater than the mean of normal myocardium were considered abnormal.[22] The extent of LGE was expressed as a percentage of total LV myocardial mass.

Patients with angina ≥3 months despite optimal medical therapy were referred for positron emission tomography (PET) scanning and were imaged using a GE Discovery VCT PET/CT system. Regional myocardial perfusion was assessed using a same day rest/stress protocol as described previously.[3,21,23,24] Attenuation-corrected PET images were reconstructed by an iterative algorithm with postprocessing filtering and static data sets analyzed using CardIQ Physio (GE Healthcare). Regional myocardial perfusion was semiquantitatively assessed from the reoriented images on different cardiac planes (short, horizontal, and vertical long axes) using the standard 17 American Heart Association segmentation, 5-point visual score method.[3] The summed stress score (SSS) and summed rest score (SRS) consisted of the summation score of the 17 LV segments during vasodilator stress and rest perfusion imaging. The summed difference score (SDS) consisted of the difference between SSS and SRS. An SDS ≥2 was considered abnormal in this study.

Data were analyzed using STATA software version 13 (StataCorp LP, College Station, Texas). Continuous variables are presented as mean ± standard deviation and categorical variables as the total number and percentage. Comparison of variables across groups was performed using analysis of variance and the chi-square or Fisher's exact test