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Role of Exercise Testing in Hypertrophic Cardiomyopathy



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ABSTRACT

Over the last 25 years, patients with hypertrophic cardiomyopathy (HCM) have been studied with a variety of methods employing physiological exercise that have made major contributions to disease management and are performed without increased risk. Previously under-utilized in HCM, exercise (stress) echocardiography has become incorporated into the standard clinical assessment and diagnostic armamentarium of HCM using upright or supine symptom-limited treadmill or bicycle modalities. In patients without outflow gradients at rest, exercise echocardiography is the most appropriate method for provoking obstruction, with the capability of predicting future development of progressive heart failure symptoms, and differentiating patients with provokable obstruction from those without obstruction, with major implications for dictating treatment options, that is, surgical myectomy (alternatively, alcohol septal ablation) versus heart transplant. Reduced myocardial oxygen consumption with metabolic (cardiopulmonary) exercise testing provides an independent and quantitative assessment of functional limitation for individual patients when the personal history is ambiguous, and also guides eligibility for heart transplant. Hypotensive blood pressure response to exercise can be an arbitrator in risk stratification decisions. Exercise testing with a variety of methods has become an integral and powerful component of the noninvasive evaluation of HCM, and in some patients can determine treatment strategy. (J Am Coll Cardiol Img 2017;10:1374-86) © 2017 by the American College of Cardiology Foundation.

Over the last 20 years, several methods of exercise testing have become an important part of patient assessment for hypertrophic cardiomyopathy (HCM) (**Central Illustration**) (1-14). However, as recently as 2002, the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for exercise testing cautioned clinicians against exercising HCM patients due to an unwarranted concern for arrhythmic risk or hemodynamic collapse (15,16). However, substantial data have now been assembled in this disease showing that exercise testing is not only safe but also a key

element in the comprehensive evaluation of HCM patients (4-14,17-23). In this contemporary review, we have taken the opportunity to assess the impact that various exercise testing methods have had on the management and prognosis of patients with HCM.

SAFETY

It is now evident, based on observations in thousands of HCM patients across the broad disease spectrum (including those with advanced heart failure or with sudden death risk) that

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exercise testing is feasible and unassociated with increased cardiovascular risk when performed in a monitored, controlled, and supervised clinical setting (4-14,17-23). Data specific to safety have been reported in 506 consecutive patients undergoing stress exercise testing from community-based or referral institutions (17,22). In the Cleveland Clinic study of 263 HCM patients, major complications occurred in <0.04%, including 1 patient with sustained ventricular tachycardia requiring cardioversion (17). In an Italian study of 243 patients, no adverse events occurred, identical to our experience in a prospective multicenter study of 320 patients with HCM designed to provoke outflow gradients with physiological exercise (5,22). There would not appear to be a compelling clinical rationale or advantage to exercise patients with substantial outflow obstruction at rest (>50 mm Hg) solely for the purpose of generating even higher gradients, given that limiting symptoms can already be attributed to the substantial gradient present at rest and the consequences of abruptly generating intracavitary left ventricular (LV) pressures >200 mm Hg is uncertain. However, in general, the exceedingly low risk associated with exercise testing is overwhelmed by the substantial information that can be acquired to benefit HCM patients. Nevertheless, caution should be observed in exercising HCM patients with implanted cardioverter-defibrillators (ICDs) to avoid unexpected provoked shocks, either appropriate or inappropriate (2,3,24).

THE PERSONAL HISTORY

Exercise testing provides critical information regarding mechanisms of functional limitation in HCM patients, as well as natural history and treatment options by replicating the type of activities in which patients engage on a daily basis. Virtually all management decisions in HCM, including the determination of candidates for invasive septal reduction therapy, are ultimately predicated on the patient's personal history of diminished functional capacity and limiting symptoms significantly impacting on quality of life. Indeed, several decades of clinical outcome data in obstructive HCM patients have demonstrated excellent improvement in heart failure symptoms and survival by surgical myectomy (or alcohol ablation), supporting the traditional strategy of qualitative assessment by personal history for recommendations to relieve outflow tract obstruction with invasive therapeutic interventions.

For these reasons, it is most useful to assess data derived from exercise testing including duration,

magnitude of provokable gradients, and peak oxygen consumption ($\dot{V}O_2$) measurements through the prism of a detailed and focused personal history, and in the context of New York Heart Association (NYHA) functional classes (1-3). This approach has the implicit advantage of assessing (albeit qualitatively) patient activity level over time and throughout the day, rather than confined to a single intense exercise testing period of 5 to 15 min.

These considerations are particularly relevant for the majority of patients with outflow tract obstruction in which the dynamic nature of gradients can cause variability with respect to onset and duration of symptoms during a variety of physical activities. However, in a clinical scenario in which symptoms and functional capacity reported by personal history are ambiguous or difficult to interpret reliably, resolution may be achieved on a case-by-case basis by adding an objective and quantitative measure of physical disability with metabolic (cardiopulmonary) exercise testing (adjusted for age and sex) (1-3).

SYMPTOM-LIMITED EXERCISE PERFORMANCE

Symptom-limited upright exercise test, performed on a treadmill (but alternatively with bicycle ergometer) has been the mainstay of exercise testing in cardiac disease, typically employed to reveal electrocardiogram evidence of myocardial ischemia and evaluate exercise tolerance (25-27). However, such stand-alone symptom-limited exercise testing has acquired a more limited role in the assessment of HCM patients for a number of reasons.

With respect to assessing myocardial ischemia, exercise testing in HCM is associated with substantial false-positive rates due to the high prevalence of pre-existing electrocardiogram abnormalities at baseline typical of this disease. In addition, a number of inconsistencies associated with exercise testing in HCM limit its role in providing a reliable assessment of overall cardiovascular functional capacity, including early and relatively common symptoms during modest and routine daily physical activities, such as walking on inclines (e.g., stairs and hills), which may not be reflected in formal treadmill exercise testing. Furthermore, traditional objective metrics, including exercise duration, % maximal predicted heart rate, and rate-pressure

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

AHA = American Heart Association

CAD = coronary artery disease

CPET = cardiopulmonary exercise test

ESC = European Society of Cardiology

HCM = hypertrophic cardiomyopathy

ICD = implantable cardioverter-defibrillator

LV = left ventricle

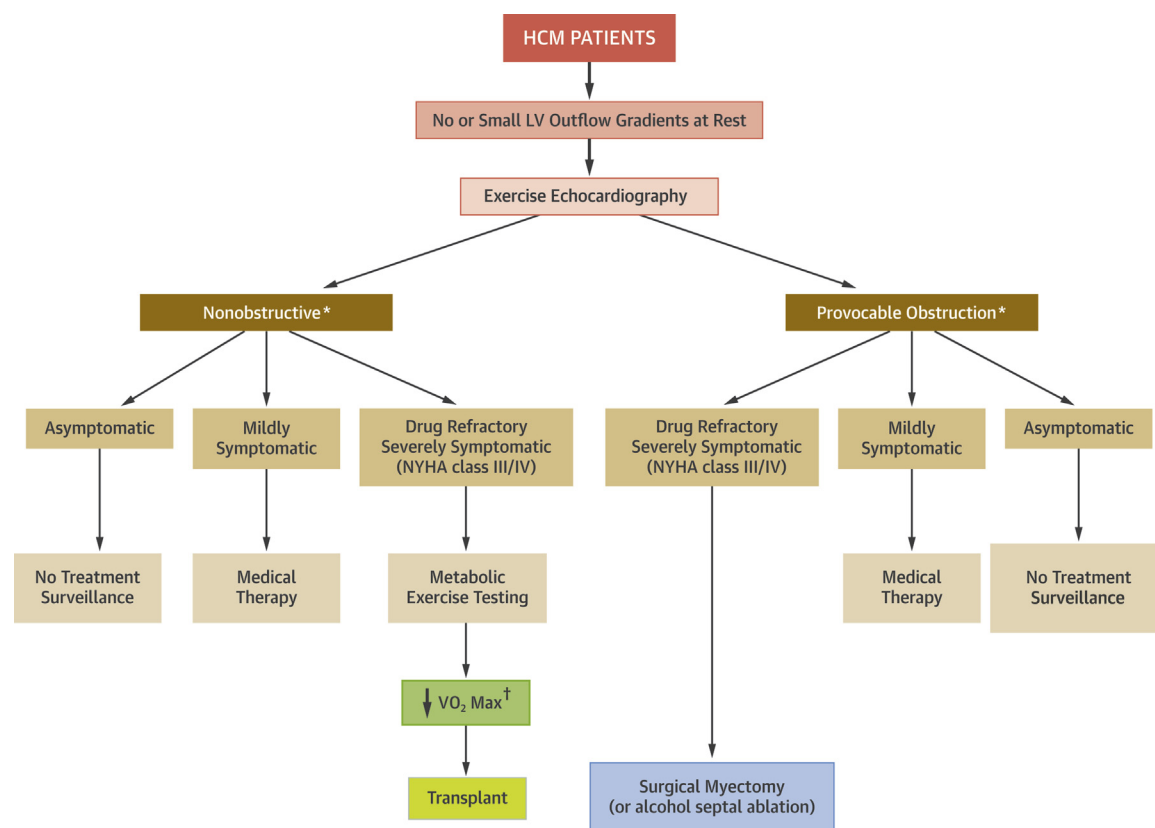
NYHA = New York Heart Association

SAM = systolic anterior motion

VE/VCO₂ = ventilation relative to CO₂ production

VO₂ = oxygen consumption

CENTRAL ILLUSTRATION Flow Diagram Summarizing Applications of Exercise Testing to Diagnosis and Management of HCM



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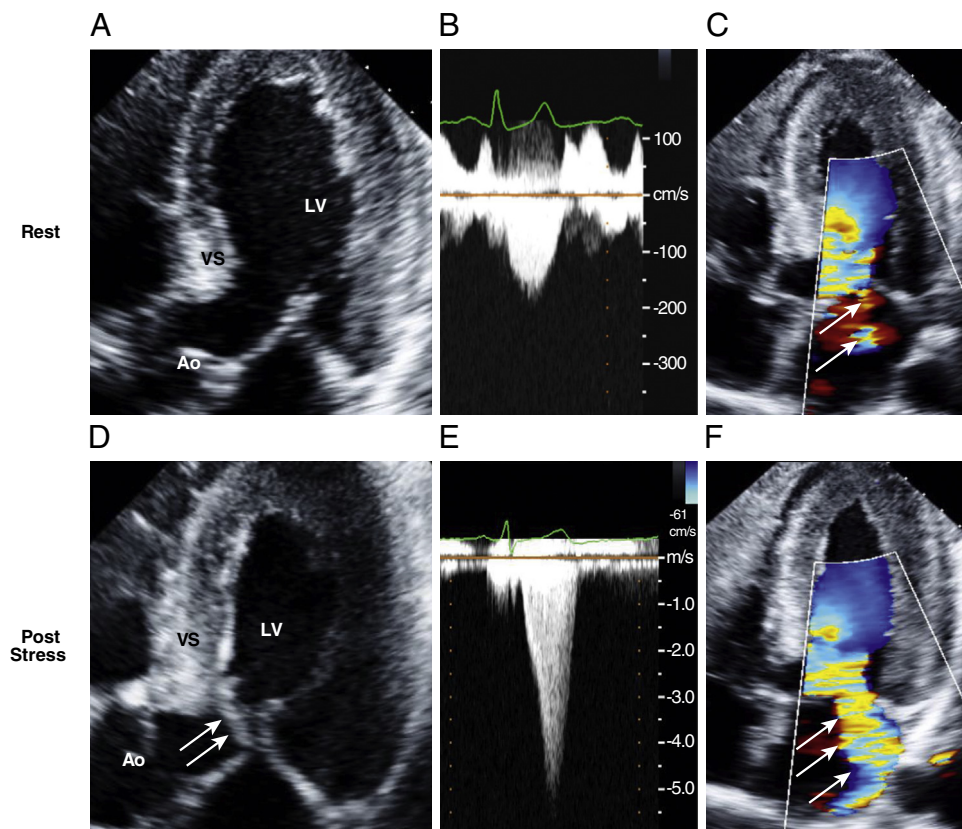
*Diagram assumes HCM patients are at low risk for sudden death and are not candidates for prophylactic implantable-defibrillators. For those HCM patients at increased risk, a sudden death primary prevention strategy may be appropriate, independent of the heart failure management strategies depicted in this figure; †VO₂ ≤14 ml/kg/min (or ≤50% predicted for age) is the conventional criterion for heart transplant listing (48), although the overall clinical profile of the patient should also be taken into account when considering listing for heart transplant. BP = blood pressure; HCM = hypertrophic cardiomyopathy; HF = heart failure; LV = left ventricular; NYHA = New York Heart Association; VO₂ Max = maximum myocardial oxygen consumption.

product at peak exercise, often paradoxically do not differ greatly in HCM patients with advanced heart failure symptoms (NYHA functional class III) compared with those in classes I or II (8,22,28-30). Such discrepancies are explained largely by the complex pathophysiology of this heterogeneous disease, which includes diastolic dysfunction, dynamic LV outflow tract obstruction (associated with mitral regurgitation), and microvascular ischemia (1,2,8,14,28-30). Finally, the results of symptom-limited exercise testing are subject to interpretation based on the pre-existing level of physical conditioning and motivation of individual patients that can influence performance (8,18-20).

EXERCISE (STRESS) ECHOCARDIOGRAPHY

CONTEXT. Combining 2-dimensional echocardiographic imaging with exercise testing has been part of general cardiovascular practice for more than 2 decades, with the distinct advantage of low cost and ease of performance in almost all laboratories. Exercise (stress) echocardiography has most commonly been employed to noninvasively raise suspicion of atherosclerotic coronary artery disease by identifying LV wall motion abnormalities (31). Although the role of exercise echocardiography in the management of HCM has historically been underappreciated (1-3), more recently this test has penetrated more fully into

FIGURE 1 Exercise Echocardiography Identifies Physiologically Provocable Outflow Obstruction in HCM Patients



Apical 5-chamber long-axis view from a 52-year-old man with hypertrophic cardiomyopathy (HCM): **(A)** at rest. Absence of systolic anterior motion (SAM) of mitral valve in mid-systole; **(B)** associated normal continuous-wave Doppler systolic velocity through left ventricular (LV) outflow tract; with **(C)** associated mild mitral regurgitation (arrows). **(D)** Immediately after exercise. Typical SAM of the mitral valve (arrows), with ventricular septal contact by anterior leaflet; **(E)** continuous-wave Doppler peak velocity of 5.0 m/s, equivalent to 100 mm Hg gradient due to SAM; **(F)** associated moderately severe and posteriorly directed mitral regurgitation jet (arrows). Ao = aorta; VS = ventricular septum.

clinical practice for this disease, primarily to measure dynamic LV outflow gradients provoked by physiological exercise usually assessed supine immediately after termination of exercise (Figure 1, Table 1) (5–8).

GRADIENT PROVOCATION. It is an important principle in HCM that severely symptomatic patients without measurable or significant outflow obstruction under resting conditions should have the opportunity to demonstrate the capacity to generate a subaortic gradient with provocation that would create treatment options to reverse heart failure with surgical myectomy (or selectively, alcohol septal ablation). Exercise under controlled conditions is the preferred gradient provocation since it comes closest to reproducing the real-life activities patients

participate in daily, and which in fact induce exertion-related symptoms that are part of the personal history.

The principle of provoking outflow gradients in HCM patients without obstruction at rest is connected historically to the first comprehensive description of the disease by the Braunwald group at the National Institutes of Health. In that early era of the 1960s, gradient provocation was carried out with a variety of nonphysiological maneuvers, including amyl nitrite inhalation, and post-premature ventricular contraction response (Brockenbrough maneuver), or sympathomimetic drugs introduced intravenously in the cardiac catheterization laboratory (32–34). However, in contrast to exercise, nonphysiological interventions may imprecisely measure, or even

TABLE 1 Studies of Prognostic Utility of Stress (Exercise) Echocardiography in HCM						
First Author (Ref. #)	Year	Cohort	Patients, n	Age, yrs	Follow-Up, yrs	Study Findings
Maron MS et al. (5)	2006	Multicenter	320	47.0 ± 17.0	—	>50% of patients without resting obstruction developed provokable LVOTO with physiological exercise.
Nistri et al. (36)	2010	Florence, Italy	74	46.0 ± 16.0	—	Earlier onset of LVOTO during physiological exercise was associated with impaired exercise performance.
Desai et al. (8)	2014	Cleveland Clinic	426	44.0 ± 14.0	8.7 ± 3.0	In asymptomatic or minimally symptomatic HCM population, patients achieving <85% predicted METs had a higher rate of combined endpoint of death, ICD discharge, or HF admission.
Finocchiaro et al. (7)	2014	Stanford	283	50.0 ± 16.0	3.5 ± 2.6	Exercise-induced LVOTO was independently associated with drug-refractory HF symptoms (HR: 5.0 [95% CI: 1.8–14.6]).
Ciampi et al. (9)	2016	Multicenter	706*	50.0 ± 16.0	4.1†	New regional wall motion abnormalities was predictive of composite endpoint. Outflow obstruction did not predict composite endpoint; development of advanced HF symptoms not evaluated.
Maron MS et al. (6)	2016	Multicenter	573	44.0 ± 17.0	6.5†	Patients with exercise-induced LVOTO were more likely to develop advanced HF symptoms compared with patients without obstruction (rate of development: 3.2% per year vs. 1.6% per year).

Values are mean ± SD. *Including 148 patients with only vasodilator stress echo. †Median.

CI = confidence interval; HCM = hypertrophic cardiomyopathy; HF = heart failure; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; LVOTO = left ventricular outflow tract obstruction; MET = metabolic equivalent; VT = ventricular tachycardia.

overestimate, true impedance to LV outflow. For example, agents such as dobutamine or isoproterenol can artificially generate or exaggerate gradients (33), and are not recommended for routine use in the 2011 U.S. (ACC/AHA) guidelines for HCM (2), although some investigators have reported isoproterenol infusion in highly selected patients (without gradients at rest) to identify candidates for septal myectomy (34). The reliability of amyl nitrite for estimating outflow gradients in the echocardiography laboratory has never been tested against a standard, but nevertheless continues to be employed in some institutions (35).

Performed simultaneously with echocardiography, the Valsalva maneuver is associated with low sensitivity but specificity approaching 100% for estimating LV outflow tract gradients (5). Specifically, normal Valsalva-induced velocities do not exclude outflow obstruction because about 50% of such patients will nevertheless generate gradients with physiological exercise. Alternatively, increased Valsalva-induced velocities consistently predict outflow gradients produced by exercise, although the magnitude of that gradient is significantly underestimated by Valsalva maneuver relative to physiological exercise (by 25 to 65 mm Hg) (5). Therefore, in selected candidates for septal reduction who cannot perform exercise echocardiography due to comorbidities, a positive Valsalva maneuver with high induced velocities can be sufficient evidence to recommend and proceed with invasive therapy to relieve gradient and heart failure symptoms.

TIMING OF GRADIENT WITH EXERCISE. Symptom-limited upright bicycle testing with echocardiography permits the serial assessment of outflow gradients *during* exercise, with the precise timing clinically relevant (36). For example, LV outflow obstruction developing rapidly at lower levels of exercise is associated with greater impairment in functional capacity and NYHA functional class compared with later onset of the gradient. Notably, gradients measured at peak exercise in the upright position and immediately following exercise (supine) show excellent correlation (36). Also, treadmill versus bicycle exercise protocols have no significant differences with regard to presence or magnitude of the induced gradients (5). Therefore, either methodology can be used to reliably provoke gradients, and according to the preference of the patient or institution.

MECHANISM. In the vast majority of HCM patients dynamic LV outflow tract obstruction is produced by systolic anterior motion (SAM) of the mitral valve with ventricular-septal contact due to a drag effect pushing the leaflets forward toward the septum, promoted by the velocity of ejection. This complex mechanism involves an interplay of reduced LV outflow tract cross-sectional area, anterior and/or posterior mitral leaflet elongation, anterior position of mitral valve and papillary muscles, and bulging contour of anterior septum into LV cavity (1-3,36,37). Occasionally, impedance to LV outflow occurs by virtue of muscular mid-cavity apposition, associated either with LV apical aneurysms or by direct insertion

of anterolateral papillary muscle into anterior mitral leaflet (1-3,36,37).

Posteriorly directed mitral regurgitation (usually mild-to-moderate) is a secondary consequence of SAM. The mitral regurgitant jet may overlap and contaminate the LV outflow jet, potentially resulting in an erroneous overestimation of the subaortic gradient (1-3,36,37). Caution and recognition of this possibility requires careful analysis of continuous-wave Doppler signal waveform morphology and timing to ensure reliable differentiation of these 2 jets (2,5,36). Doppler systolic flow patterns representative of LV outflow gradients characteristically demonstrate a gradual increase in velocity in early systole with mid-systolic acceleration and peaking (“dagger-shaped”). By contrast, the mitral regurgitation signal begins abruptly at the onset of systole and rapidly establishes markedly increased velocity (usually >6 m/s), which then persists throughout systole (“bell-shaped”) (2,5,36).

LV outflow gradients in HCM are considered dynamic, given the characteristic spontaneous variability day-to-day (if not hour-to-hour), also potentially influenced in some patients by hydration, meals, or alcohol (1,32,38–41). Therefore, caution is advised in making major clinical decisions based on only a single Doppler study when a gradient is absent in patients with limiting symptoms. In such contradictory clinical situations, consideration should be given to repeating the exercise echocardiogram, preferably while temporarily withholding atrioventricular nodal blocking drugs, potentially with alternative exercise methodology (treadmill or bicycle). This is particularly important since the presence of outflow gradients create treatment options not available to nonobstructive patients (1-3).

PREDICTING CLINICAL COURSE. The clinical course of HCM is diverse and often unpredictable. However, because HCM is now associated with effective contemporary treatment options capable of substantially reducing disease-related mortality, identifying clinical markers that anticipate patient outcome has become a priority. Indeed, over the last 2 decades, predictors of arrhythmic sudden death have been identified (including some associated with exercise), leading to an advanced risk stratification algorithm, and more appropriate selection of high-risk patients for primary prevention of sudden death with implantable defibrillators (4,42). However, markers predicting heart failure progression have been more limited, for example, to LV outflow tract obstruction under resting (basal) conditions (43), left atrial dimension, or extensive

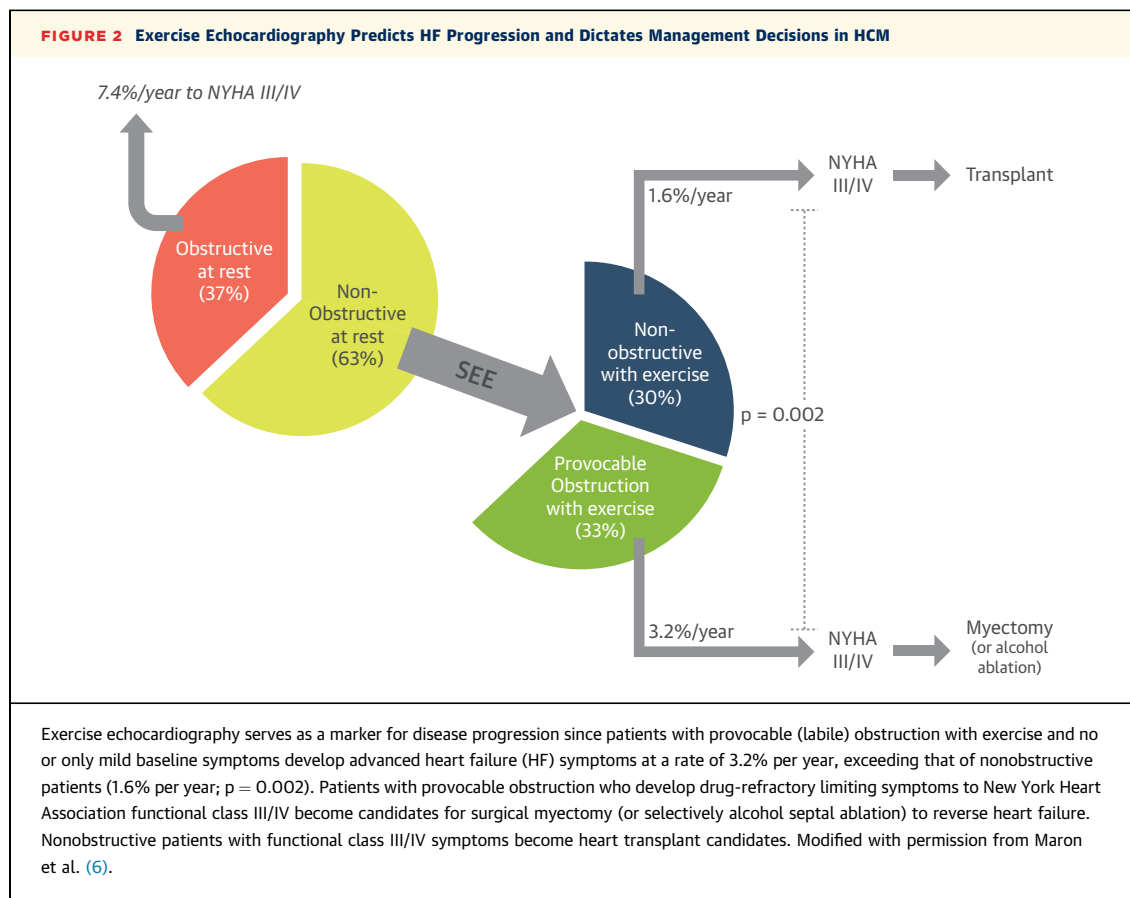
late gadolinium enhancement in patients without obstruction (44,45).

Since 2003, it has been our routine practice to use echocardiography in conjunction with a symptom-limited Bruce protocol and upright treadmill (or bicycle ergometer) exercise in patients with no or only small outflow gradients at rest, whether or not symptomatic (5,6). Notably, exercise provoked gradients in patients without significant exertional symptoms served as a baseline marker for predicting future risk of heart failure progression to NYHA functional class III/IV (Figure 2) (6). Of 220 consecutive patients with provokable obstruction but no significant exertional symptoms, rate of progression to NYHA functional class III/IV symptoms over 6.5 ± 2.0 years was 3.2%/year, 2-fold greater compared with the rate of progression to severe symptoms in non-obstructive patients without gradients at rest or with provocation (1.6%/year) (Figure 3) (6).

MANAGEMENT IMPLICATIONS. In patients without outflow obstruction at rest who develop severe symptoms, exercise echocardiography alone has the capacity to dictate major management decisions. Identifying those patients with large physiologically provokable gradients (≥ 50 mm Hg) creates the opportunity for surgical myectomy (or alternatively, alcohol septal ablation) and provides the potential for heart failure reversal, improved quality of life, and a survival benefit. Indeed, in one study, about 75% of the latter patients with symptomatic provokable obstruction underwent myectomy, with improvement to class I or II in about 95%. These observations also underscore the principle that surgical myectomy is not confined to those patients with large resting gradients (1-4), and in fact should be considered in all severely symptomatic patients with LV outflow obstruction (including those with physiologically provokable gradients).

By contrast, when exercise echocardiography does not provoke a significant subaortic gradient (i.e., nonobstructive HCM) (5), future management is confined to heart transplant as the only definitive long-term treatment option to reverse refractory heart failure (1-4). Therefore, exercise echocardiography is the single test in symptomatic patients without rest obstruction that has the power to reliably differentiate 2 very different management strategies, that is, myectomy (or alternatively, alcohol ablation) with inducible gradient, or heart transplant without obstruction.

DRUG TREATMENT. Drugs conventionally employed to control symptoms in HCM have little or no effect on resting outflow gradients with the possible



exception of disopyramide. However, in some HCM patients, exercise-induced gradients can be blunted (or prevented) pharmacologically with beta-blocker administration, a principle known from the early 1960s (32). In one study, provokable gradients were reduced by treatment with beta-blockers from 87 mm Hg to 36 mm Hg on average over a ≥ 8 -month period, including abolition of outflow obstruction in 50% (46). This observation provides an option for early treatment of physically active patients with provokable gradients, using standard doses of beta-blockers aimed at reducing the hemodynamic burden of elevated LV pressures. However, data are not available that support the efficacy of drug therapy to mitigate progression to severe heart failure symptoms in patients with obstruction.

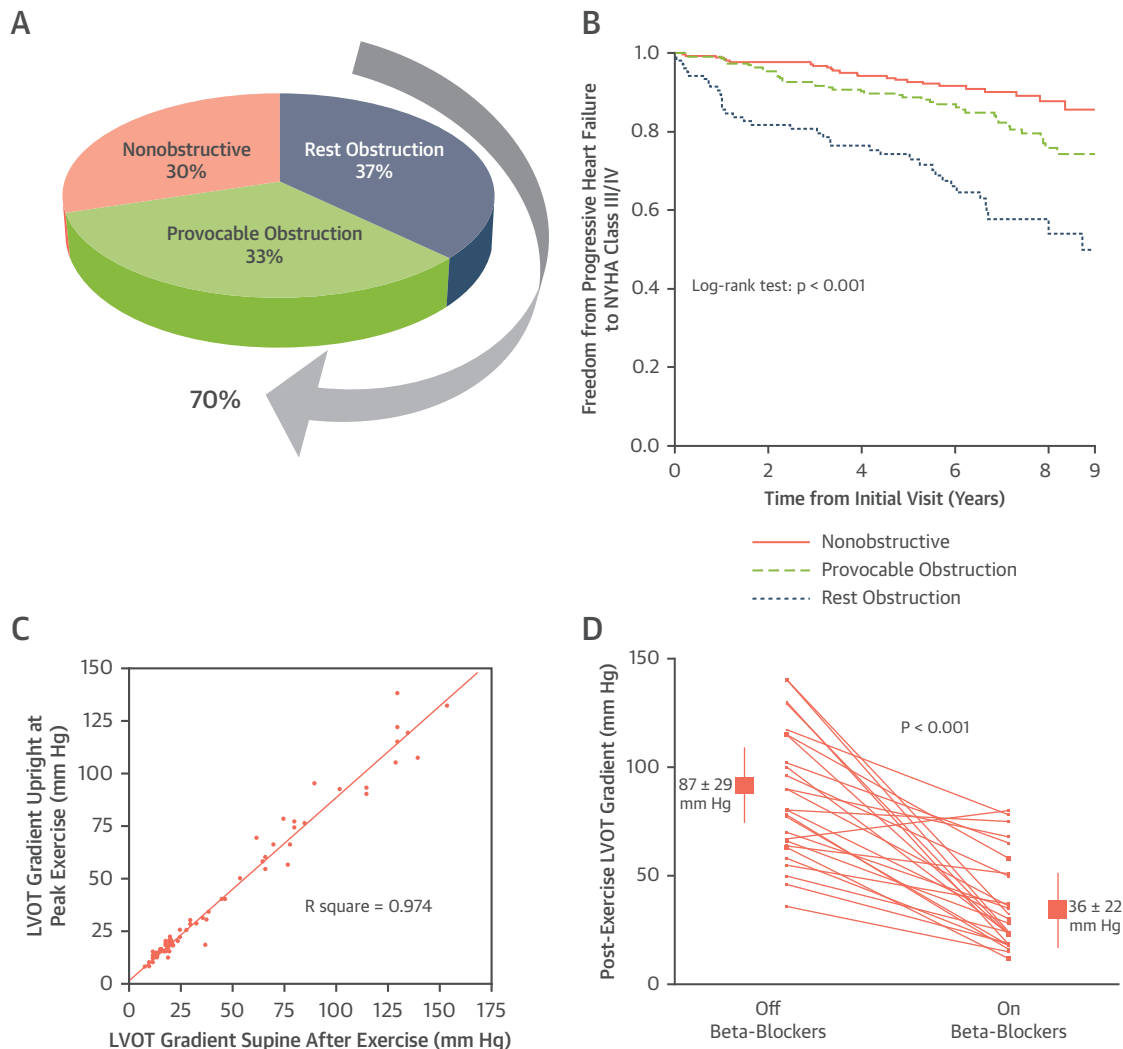
FAMILY MEMBERS. The value of exercise echocardiography in assessing asymptomatic family members genotyped to pathogenic sarcomere mutations, but without LV hypertrophy (genotype positive/phenotype negative), is limited given the low likelihood of provoking gradients due to SAM in the absence of basal septal hypertrophy (2,3).

In patients with borderline or mildly increased LV wall thickness (i.e., 13 to 15 mm), an exercise-induced outflow gradient due to SAM represents a morphological marker that supports the clinical diagnosis of HCM.

METABOLIC EXERCISE TESTING

Cardiopulmonary exercise testing (CPET) is an established clinical tool used in the management of a variety of cardiac disorders (15,20). In patients with congestive heart failure, metabolic parameters such as peak myocardial oxygen consumption with maximal exercise ($\dot{V}O_2$) identifies high-risk individuals requiring close monitoring as potential heart transplant candidates, and also with the potential of differentiating cardiac from pulmonary dyspnea (10-14,47). For this reason, metabolic (cardiopulmonary) testing with peak $\dot{V}O_2$ is considered an objective method for assessing exercise capacity in patients with ischemic or nonischemic heart failure (48). Given the strong association with increased heart failure mortality in patients with peak $\dot{V}O_2 \leq 14$ ml/kg/min

FIGURE 3 Significance of LV Outflow Tract Gradients in HCM



(A) Prevalence of LV outflow obstruction in HCM patients. Patients with rest and physiologically provokable obstruction together comprise 70% of all HCM patients in a tertiary care center population, although one-third are only identifiable with exercise. **(B)** Freedom from progression to advanced heart failure symptoms (NYHA functional class III/IV) in 573 HCM patients with no or mild symptoms at baseline, comparing nonobstructive HCM, rest obstruction, and obstruction with exercise provocation. Greatest likelihood of progressive heart failure symptoms is associated with rest obstruction, although patients with provokable gradients were 2-fold more likely to develop severe symptoms compared to patients without obstruction. **(C)** Scatterplot demonstrating excellent correlation between subaortic gradients measured at peak exercise in upright position and immediately following exercise supine. **(D)** Effect of beta-blocker therapy on provokable outflow gradients with exercise. Outflow gradients following treatment with a beta-blocker are greatly reduced by 51 ± 34 mm Hg compared with pre-treatment. **A** reproduced with permission from Maron et al. (5); **B** reproduced with permission from Maron et al. (6); **C** reproduced with permission from Nistri et al. (36); **D** reproduced with permission from Nistri et al. (46). Abbreviations as in Figures 1 and 2.

(or $\leq 50\%$ of predicted in patients < 50 years of age), the International Society for Heart and Lung Transplantation has given substantial weight to this maximum oxygen consumption cutoff in guiding eligibility for heart transplant listing (48).

In HCM, numerous cross-sectional studies have demonstrated that peak \dot{V}_{O_2} correlates with a number

of clinically relevant variables, including severity of diastolic function (29,30), quality of life (28), and (inversely) with outflow tract gradient (49). Also, intervention with myectomy or alcohol ablation to relieve outflow obstruction, a major determinant of heart failure symptoms in HCM, is associated with improved peak \dot{V}_{O_2} (50).

TABLE 2 Studies of Prognostic Utility Using Metabolic (Cardiopulmonary) Exercise Testing in HCM

First Author (Ref. #)	Year	Institution	Patients, N	Age, yrs	% Obstructive	Follow-Up, yrs	Variables Associated With Endpoint	Endpoint
Sorajja et al. (12)	2012	Mayo	182	53 ± 15	100	4.0 ± 3.0	$\dot{V}O_2$	HF progression; death
Finocchiaro et al. (11)	2015	Stanford	156	51 ± 14	62	2.3 ± 0.9	$\dot{V}O_2$; VEI	Composite
Masri et al. (13)	2015	Cleveland Clinic	1,005	50 ± 14	85	5.5 ± 4.0	$\dot{V}O_2$	Composite
Coats et al. (10)	2015	London	1,898	47 ± 15	31*	5.6†	$\dot{V}O_2$; VEI; AT	All cause-mortality; transplant
Magri et al. (47)	2016	Multicenter	623	49 ± 16	32*	3.7†	VEI	Sudden death
Magri et al. (14)	2016	Multicenter	620	49 ± 16	32*	3.8†	$\dot{V}O_2$; VEI	HF progression

Values are mean ± SD unless otherwise indicated. *Does not include patients with provokable obstruction. †Median.
AT = anaerobic threshold; HF = heart failure; VEI = ventilatory efficiency; $\dot{V}O_2$ = oxygen consumption.

Furthermore, there are now substantial published reports relating CPET data to outcome in >3,000 HCM patients reported from several major centers (Table 2) (10-14). In a study by Sorajja et al. (12) confined to patients with outflow obstruction and no or only mild symptoms, reduced peak $\dot{V}O_2$ (expressed as % predicted peak oxygen consumption), was associated with increased risk for the combined endpoint of progression to advanced heart failure and total mortality (Figure 4). Ventilation relative to CO₂ production (VE/VCO₂), a marker of ventilatory efficiency, was not prognostic of these adverse endpoints (12). However, a study by Coats et al. (10) identified peak $\dot{V}O_2$, as well as submaximal exercise parameters (i.e., ventilator efficiency and anaerobic threshold), as predictive of all-cause mortality or progression to heart transplant. Finocchiaro et al. (11), as well as a multicenter study of 5 Italian institutions by Magri et al. (14), reported a significant relationship between submaximal exercise parameters and adverse outcome using a composite endpoint of total mortality, heart transplantation, and also progressive heart failure due to outflow obstruction (11,14). On the basis of these studies, all highly dependent on multivariate analysis and composite endpoints, low peak $\dot{V}O_2$ has been promoted as an independent predictor for major adverse events in HCM, with normal peak $\dot{V}O_2$ most consistent with favorable clinical outcome (10-14).

Nevertheless, there are a number of factors that influence interpretation of CPET data in HCM that deserve consideration here. First, most of the cohort investigations have combined patients with and patients without LV outflow tract obstruction, and have also included some patients who have had already expressed advanced symptoms at the time of CPET examination. In addition, the practice of using combined clinical endpoints, and of pooling different disease pathways (e.g., such as heart failure, sudden death, and total mortality) creates challenges in discerning precisely which future adverse events are

in fact predicted by low $\dot{V}O_2$ measurements, and ultimately, translating test results to specific management strategies for individual patients.

Furthermore, $\dot{V}O_2$ values obtained across the broad spectrum of HCM patients show considerable variability, with low values predominant in 70% (<80% of age predicted). Therefore, given this frequency of abnormal $\dot{V}O_2$, using CPET and peak $\dot{V}O_2$ alone as a reliable binary prognostic marker with the potential to impact clinical management decisions can be problematic. On the other hand, because peak $\dot{V}O_2$ provides a quantitative measure of functional capacity, it represents a reproducible clinical marker for studying the effect of therapeutic interventions. Consequently, peak $\dot{V}O_2$ has been used widely as a clinical endpoint in heart failure trials designed to assess the efficacy of emerging treatment interventions (25), including those proposed for approval by regulatory agencies such as the Food and Drug Administration.

Challenges in translating CPET results into individual HCM patient management strategies is underscored in those with severe symptoms from outflow tract obstruction for whom decisions regarding myectomy (or alcohol septal ablation) have been largely based on assessment of NYHA functional class by personal history, a strategy supported by the 2011 ACC/AHA management guidelines (2). The validity of this practice focused on the personal history is confirmed by the experience over the last 40 years in which patients have been referred for invasive septal reduction treatment to reverse heart failure, based on a history of significant daily functional limitation, and who have subsequently experienced restoration of normal or near-normal quality of life after relief of outflow obstruction.

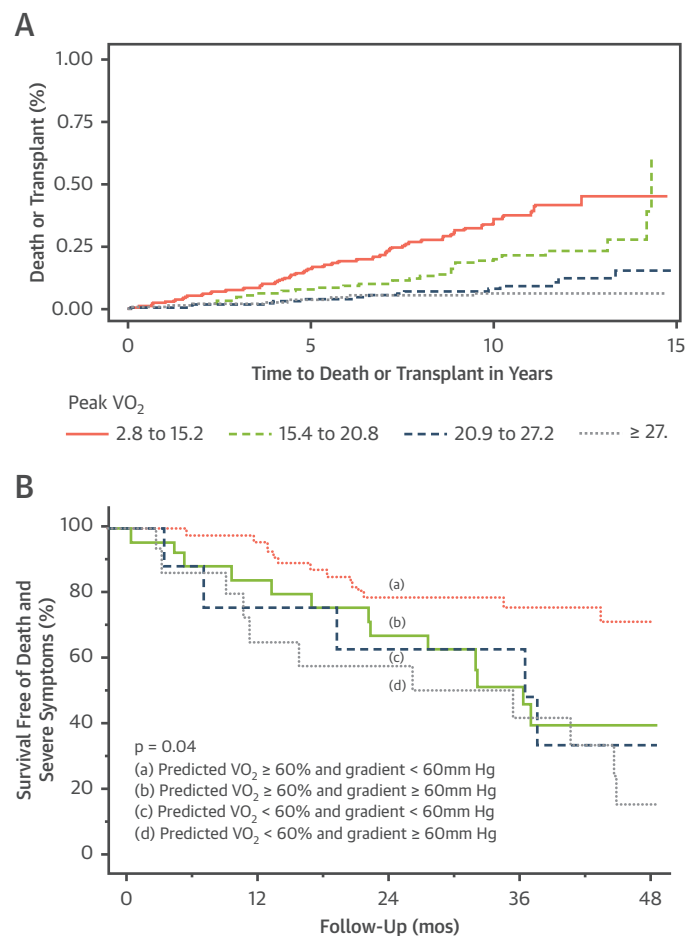
Recent European Society of Cardiology (ESC) treatment guidelines for HCM recommend that CPET be considered for all HCM patients undergoing invasive septal reduction therapy to assess severity of

symptom limitation (3). However, a challenge remains in translating these broad ESC recommendations for CPET to guide management in different subgroups within the diverse HCM patient population. For example, presently, there are no data to support using peak $\dot{V}O_2$ to either justify earlier invasive intervention for obstructive HCM patients with relatively mild symptoms, nor are there clinically relevant (but arbitrary) cutpoints for abnormal $\dot{V}O_2$ that could be applied to individual patients for the purpose of making management decisions. Therefore, severely limited patients by history, with unexpectedly normal (or near-normal) metabolic parameters, should not be excluded from septal reduction therapy to relieve outflow obstruction. Nevertheless, if after a detailed patient history, ambiguity remains regarding the true level of disability in an individual HCM patient, CPET may be valuable on a case-by-case basis in providing objective and quantitative evidence supporting (or excluding) impaired functional capacity.

For nonobstructive patients with unrelenting end-stage heart failure symptoms, CPET is a mandatory component of the targeted heart transplant evaluation, with peak $\dot{V}O_2 \leq 14$ ml/kg/min (or $\leq 50\%$ predicted for age) as the primary metric to determine candidacy (48). However, paradoxically, some end-stage nonobstructive HCM patients who are candidates for transplant, as the only viable therapeutic option with potential to restore acceptable quality of life, may have peak $\dot{V}O_2 > 14$ ml/kg/min. In our experience, some such patients have been denied transplant listing status (51) for failing to meet the prescribed criteria established by the International Society for Heart and Lung Transplantation (48), even though metabolic exercise testing does not reliably reflect the symptom limitation experienced on a daily basis. This paradox likely results because heart failure in HCM in the absence of outflow obstruction is multifactorial, usually involving impaired LV filling with low cardiac output, microvascular ischemia, extensive myocardial fibrosis, and pulmonary hypertension. Therefore, the decision to pursue heart transplant in patients with nonobstructive HCM should take into account the overall clinical profile, including the results of metabolic exercise testing, but with the predominant weight placed on the clinical assessment of symptoms by history.

CPET maximum peak oxygen consumption can be useful in distinguishing HCM with relatively mild LV hypertrophy from physiological hypertrophy (i.e., athlete's heart) (52). For individual athlete-patients within an ambiguous diagnostic "grey zone," based on conventional imaging markers, a peak $\dot{V}O_2 > 50$ ml/kg/min

FIGURE 4 Metabolic (Cardiopulmonary) Stress Testing Predicts Adverse Events in HCM



(A) Kaplan-Meier analysis showing cumulative hazard rates of death/transplant in 1,898 patients with HCM undergoing cardiopulmonary stress testing and stratified according to quartiles of peak oxygen consumption (peak $\dot{V}O_2$) (11). **(B)** Survival free of death or development of severe symptoms according to percentage of predicted peak $\dot{V}O_2$ in 182 patients with obstructive HCM and no or minimal baseline symptoms (12). **A** reproduced with permission from Coats et al. (10); **B** reproduced with permission from Sorajja et al. (12). HCM = hypertrophic cardiomyopathy.

(or $>20\%$ above the predicted maximum) is most consistent with athlete's heart and is nondiagnostic of HCM (2,3,52).

RISK STRATIFICATION

Assessment of risk level for sudden death in HCM is predicated on a composite of noninvasive clinical markers including 2 related to exercise. First, exercise-related (but unexplained) syncope is a primary risk marker in HCM. One or more events can be the basis of a recommendation for an ICD and has

been shown to be the single risk factor most commonly associated with an ICD intervention (2). Second, the hypotensive blood pressure response to exercise can be a risk factor in accord with the 2011 U.S. (ACC/AHA) guidelines for HCM management (2). This marker, occurring in 20% to 40% of HCM patients, is defined either as a hypotensive or an attenuated response to exercise (<20 mm Hg from baseline) and is generally conceded to be the weakest and least reliable of the traditional major risk markers (21,23,53,54), particularly in patients with dynamic outflow obstruction (2,3,21,23).

In this regard, based on the data of Olivotto et al. (21), the hypotensive blood pressure response to exercise is associated with low positive but high negative predictive accuracy, and therefore is most useful for identifying lower-risk patients. This marker rarely forms the sole basis for a primary prevention ICD recommendation in the absence of other conventional evidence of increased risk (21), but can more often serve as a decision arbitrator in ambiguous risk situations. The weak predictive value for sudden death events, and the absence of a clear mechanistic link between this abnormal vascular response and potentially lethal ventricular tachyarrhythmias, has resulted in limited use of the blood pressure response to exercise in the practice of HCM risk stratification (1-3,42).

There are conflicting data regarding CPET and the prediction specifically of sudden cardiac death in HCM. Although Magri et al. (47) reported that VE/VCO_2 was an independent predictor of sudden death events in a study of 623 HCM patients, these data are in sharp contrast to those in the larger study ($N = 1,898$) of Coats et al. (10), who found that neither peak $\dot{V}O_2$ nor VE/VCO_2 predicted sudden death events. Consequently, neither VE/VCO_2 nor $\dot{V}O_2$ are currently used in risk stratification.

EVALUATION OF EPICARDIAL CORONARY ARTERY DISEASE

Chest pain is a common symptom occurring in at least 25% of HCM patients (1-3), either prolonged and atypical at rest, but also consistent with classic angina pectoris provoked with exertion. Chest pain in HCM is likely due to microvascular ischemia (associated with structurally abnormal intramural coronary arterioles), increased oxygen demand on the hypertrophied myocardium, or compressive systolic deformation of arterioles and impaired LV relaxation that contribute to coronary flow derangement. (1-3,55).

Epicardial coronary artery disease (CAD) conveys an increased mortality risk in patients with HCM (56).

However, single-photon emission computed tomography, the most common physiological exercise test employed for detection of myocardial ischemia in patients with CAD, lacks diagnostic specificity in the presence of HCM, although with acceptable negative predictive value (57,58). Also, given that perfusion defects (both fixed and reversible) have been reported in about 50% of young HCM patients, it is apparent that false-positive tests suggestive of ischemia greatly exceed the expectation for epicardial CAD in this population, thereby reducing the diagnostic utility in HCM (58).

Similarly, limitations in recognition of CAD in HCM patients arise with exercise echocardiography because LV wall motion abnormalities are evident in up to 50% of HCM patients (59). Therefore, coronary angiography remains the preferred test for symptomatic HCM patients at moderate-to-high risk for epicardial CAD. Computed tomography angiography offers a noninvasive alternative to exclude significant epicardial CAD in lower-risk HCM patients, based on high negative predictive value (but lower false-positive rates) compared to myocardial perfusion stress imaging (2,3,57,58,60).

Although not a widely used clinical test, and lacking penetration into routine practice for HCM, positron emission tomography offers quantification of myocardial blood flow, a potential marker for microvascular dysfunction in the absence of epicardial CAD (61). In HCM, positron emission tomography studies have demonstrated that the administration of vasodilators blunts myocardial blood flow, and that patients with the greatest impairment are at the highest risk for cardiovascular mortality and advanced heart failure (61).

CONCLUSIONS

Exercise testing, once considered to be potentially deleterious in HCM, has now become part of the comprehensive clinical evaluation leading to a more reliable assessment of natural history and effective treatment options (1-4). Metabolic exercise testing can provide a quantitative assessment of functional limitation (1-14), with maximum $\dot{V}O_2$ a potential predictor and arbitrator for therapeutic decision-making in symptomatic patients with and without obstruction. However, it is most common in clinical practice to rely on the personal history (in accord with NYHA functional class) to assess the level of disability and resolve management decisions including those for surgical septal myectomy.

Importantly, exercise echocardiography has the power to predict future development of progressive

heart failure symptoms and also reliably differentiate nonobstructive HCM patients from those with provokable (labile) gradients, that is, dictate very different major management strategies for the individual patient, such as myectomy for those with gradients versus heart transplant for those without gradients. Together, these observations support the expansive use of exercise testing in HCM to clarify prognosis and management

options, now, particularly relevant in the current contemporary treatment era for this complex genetic disease.

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