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## Hypertrophic Cardiomyopathy Is Predominantly a Disease of Left Ventricular Outflow Tract Obstruction

Martin S. Maron, MD; Iacopo Olivotto, MD; Andrey G. Zenovich, MSc; Mark S. Link, MD; Natesa G. Pandian, MD; Jeffery T. Kuvin, MD; Stefano Nistri, MD; Franco Cecchi, MD; James E. Udelson, MD; Barry J. Maron, MD

**Background**—Nonobstructive hypertrophic cardiomyopathy (HCM) has been regarded as the predominant hemodynamic form of the disease on the basis of assessment of outflow gradient under resting conditions. We sought to prospectively define the prevalence, clinical profile, and significance of left ventricular (LV) outflow tract obstruction under resting conditions and with physiological exercise in a large HCM cohort.

**Methods and Results**—We prospectively analyzed 320 consecutive HCM patients (age,  $47 \pm 17$  years), measuring LV outflow gradient at rest, with Valsalva maneuver, and with exercise echocardiography. LV outflow obstruction was present at rest and/or with exercise in 225 patients (70%); 119 had rest gradients  $\geq 50$  mm Hg and were not exercised. Of the other 201 patients with gradients  $< 50$  mm Hg at rest (average,  $4 \pm 9$  mm Hg), 106 developed mechanical obstruction to LV outflow resulting from mitral valve–septal contact after exercise ( $80 \pm 43$  mm Hg), including 76 with marked gradients  $\geq 50$  mm Hg and 46 with heart failure symptoms. The remaining 95 patients (30%) had no or small gradients ( $< 30$  mm Hg) both at rest and with exercise. Valsalva maneuver underestimated the presence and magnitude of exercise-induced obstruction.

**Conclusions**—Among those patients who come to clinical evaluation, HCM is a predominantly obstructive disease in which LV outflow gradients, frequently associated with heart failure symptoms and often identified only with exercise, are evident in most patients (ie, 70%). Identification of LV outflow obstruction with exercise echocardiography may broaden management options in HCM by identifying symptomatic patients not otherwise regarded as potential candidates for septal reduction therapy. Assessment of subaortic gradients with exercise should be a routine component of the evaluation of HCM patients without outflow obstruction under resting conditions. (*Circulation*. 2006;114:2232-2239.)

**Key Words:** cardiomyopathy ■ echocardiography ■ exercise ■ heart failure ■ imaging  
■ Valsalva ■ ventricular outflow obstruction

Obstruction to left ventricular (LV) outflow is an important pathophysiological component of hypertrophic cardiomyopathy (HCM).<sup>1-14</sup> When present under resting (basal) conditions, obstruction in HCM is an independent predictor of adverse clinical consequences such as progressive heart failure and cardiovascular death.<sup>13,14</sup> Moreover, the presence of significant subaortic gradients identifies a subgroup of patients in whom septal reduction interventions such as surgical myectomy or alcohol septal ablation may be considered therapeutic options.<sup>6,8</sup>

ocations remain a source of controversy and have not been subjected to systematic analysis.<sup>2-5,7,11,12,15-17</sup> Indeed, HCM generally has been regarded as a predominantly nonobstructive disease on the basis of observations made under basal conditions.<sup>6,8,13</sup> Therefore, in the present investigation, we have prospectively studied a large consecutive cohort of HCM patients to define the prevalence, clinical profile, and significance of LV outflow obstruction at rest and with physiological exercise.

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However, although much attention has been directed toward mechanical impedance to LV outflow at rest, the frequency and significance of dynamic subaortic gradients induced with prov-

### Methods

#### Study Population

A total of 448 HCM patients were prospectively evaluated between July 2003 and November 2004 at 3 referral centers: Tufts-New England Medical Center, Boston, Mass (n=105); Minneapolis Heart Institute Foundation, Minneapolis, Minn (n=143), and Azienda

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Ospedaliera Careggi, Florence, Italy (n=200). Of these 448 patients, 128 were judged ineligible for exercise testing and were excluded from the study for the following reasons: particularly advanced age or heart failure symptoms resulting from the "end-stage" phase with systolic dysfunction,<sup>6,18</sup> prior septal myectomy or alcohol septal ablation, excessive arrhythmic risk with prior documentation of ventricular tachyarrhythmias related to activity, recent exertional syncope, comorbid medical conditions that prohibited reliable exercise testing (eg, severe peripheral vascular and obstructive pulmonary diseases), coexistent aortic stenosis, pregnancy, or failure to provide informed consent.

Therefore, the final study group consisted of 320 HCM patients, of whom 201 performed standard exercise testing with echocardiography. Patients with gradients at rest  $\geq 50$  mm Hg (n=119) did not undergo exercise testing, given the lack of clinical significance attributable to higher gradients in such patients and the potential cardiovascular risks.

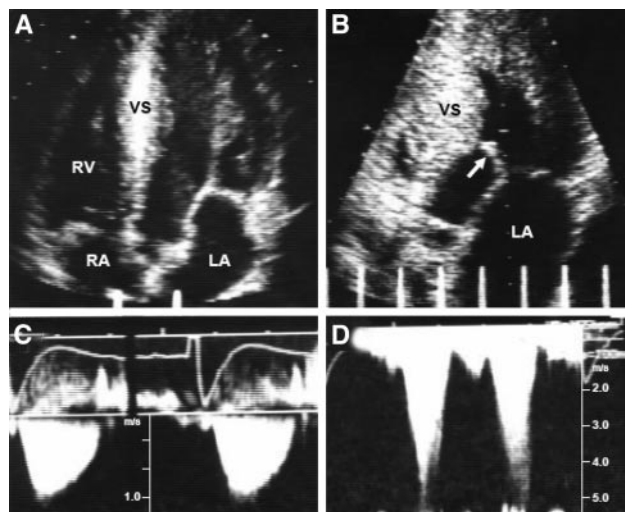
Compared with the overall study cohort (n=320), the 128 patients excluded from the analysis as ineligible for exercise testing were older (51 versus 47 years;  $P=0.02$ ), were more symptomatic (mean New York Heart Association [NYHA] class 2 versus 1.5;  $P<0.0001$ ), and had lower gradients at rest (5 versus 32 mm Hg;  $P<0.0001$ ) but did not differ with regard to maximal LV wall thickness (22 versus 22 mm;  $P=0.6$ ) or LV end-diastolic dimension (44 versus 43 mm;  $P=0.3$ ). All patients enrolled in the study signed a statement, previously approved by the Institutional Review boards of the Allina Health System and Tufts-New England Medical Center or conforming to the Authority for Privacy Act in Italy, agreeing to the use of their medical information for research purposes. The authors had full access to the data and take responsibility for their integrity. All authors have read and agree to the manuscript as written.

### Resting Echocardiography

Standard echocardiographic studies were performed under basal conditions with commercially available instruments. Clinical diagnosis of HCM was based on the demonstration by 2-dimensional echocardiogram of a hypertrophied and nondilated LV (wall thickness  $\geq 13$  mm in adults) in the absence of another cardiac or systemic disease capable of producing a similar degree of hypertrophy.<sup>6,8,9,19</sup> Magnitude and distribution of LV hypertrophy were assessed as previously described.<sup>19-21</sup>

The peak instantaneous LV outflow tract gradient was measured at rest and during the strain phase of the Valsalva maneuver (in the left lateral decubitus position) with continuous-wave Doppler interrogation directly parallel to the outflow tract in the apical 5-chamber view under direct visualization. The mitral regurgitation jet was then interrogated separately. In obstructive HCM, the continuous-wave Doppler systolic flow pattern of dynamic subaortic obstruction demonstrates a gradual increase in velocity in early systole with midsystolic acceleration and peaking. In contrast, the mitral regurgitation signal begins abruptly at the onset of systole, rapidly establishing a markedly increased velocity (usually  $>6$  m/s), which persists throughout systole. Difficulty in interpretation not uncommonly arises when the outflow tract and mitral regurgitation jets overlap and become superimposed because of their close anatomic proximity within the small outflow tract area characteristic of HCM.

Therefore, at baseline in each patient, the investigators routinely analyzed and compared continuous-wave Doppler signals and waveform shapes (and timing) from these 2 sources to accurately distinguish between each of the 2 jets. Care was taken to report only those gradients derived from Doppler velocity profiles typical of subaortic obstruction (caused by systolic anterior motion [SAM] of the mitral valve) that avoided contamination by the mitral regurgitation jet.<sup>13,22</sup> SAM of the mitral valve was graded semiquantitatively from the 2-dimensional image or derived M-mode recordings using the grading system previously described.<sup>23</sup> Subaortic obstruction was defined as mechanical impedance to outflow resulting from mitral valve–ventricular septal contact (or near contact) in midsystole; no patient considered for this study showed muscular midcavity obstruction resulting from apposition of the ventricular septum and



**Figure 1.** Apical 5-chamber long-axis view at rest showing mitral valve at end diastole (SAM was absent in systole) (A) with normal continuous-wave Doppler velocity through the LV outflow tract (C). In the same patient, immediately after exercise, the identical view demonstrates typical SAM-septal contact (B, arrow) with a corresponding continuous-wave Doppler velocity of 5 m/s (100 mm Hg) (D).

lateral free wall or from direct anomalous papillary muscle insertion into the anterior mitral leaflet (in the absence of SAM).<sup>6,8,24-26</sup>

### Exercise Echocardiography

Patients selected for maximal symptom-limited exercise echocardiography (with a basal gradient  $<50$  mm Hg) were instructed to withhold all cardioactive medications 24 to 72 hours before both the rest echocardiogram (with Valsalva) and subsequent exercise testing. In 20 patients, it was judged imprudent to discontinue drug therapy because of dependence on medications to control symptoms:  $\beta$ -blockers (n=16), angiotensin-converting enzyme inhibitors (n=3), and disopyramide (n=1). After the baseline (resting) echocardiogram was obtained in patients in the supine position, an upright treadmill (n=126) or bicycle (n=75) exercise test consistent with customary practice in US or European centers, respectively, was performed using a standard Bruce or ergometer<sup>27</sup> protocol. Patients were encouraged to perform maximally to achieve their expected heart rate. A 12-lead ECG, blood pressure, and heart rate were recorded at rest and at 3-minute intervals during exercise. Exercise was terminated when the target heart rate (85% of peak age-predicted heart rate) was achieved (n=178, 89%) or when fatigue, dyspnea, chest pain, or marked hypotension intervened (n=23, 11%). No adverse events occurred during exercise testing.

After exercise, patients were immediately placed in the left lateral decubitus position, and peak instantaneous LV outflow tract velocities were measured again in the apical view (Figure 1). The time from termination of exercise to recording of the LV outflow gradient was calculated with a stopwatch. Immediately after each gradient was recorded, the degree of SAM and mitral regurgitation was assessed in the apical and/or parasternal long-axis views.

For convenience, selected data are presented with the gradients elicited with exercise segregated into 2 hemodynamic subgroups: with obstruction ( $\geq 50$  mm Hg and 30 to 49 mm Hg) and the nonobstructed group ( $<30$  mm Hg). These cutoffs were selected on the basis of current knowledge and treatment guidelines for HCM; ie, gradients  $\geq 50$  mm Hg represent the generally accepted minimum for recommending an invasive intervention,<sup>6,8</sup> and gradients  $\geq 30$  mm Hg have been shown to be responsible for heart failure progression and cardiovascular mortality when assessed under basal conditions.<sup>13,14</sup> An abnormal blood pressure response was defined as a systolic blood pressure that decreases or does not increase  $\geq 25$  mm Hg from baseline.<sup>28,29</sup>

## Statistical Analysis

Data are expressed as mean±SD. Two-tailed Student's *t* test or 1-way analysis of variance was used to compare normally distributed data. The  $\chi^2$  (and when applicable Yate's corrected  $\chi^2$ ) tests were used to compare noncontinuous variables expressed as proportions. Predictors of exercise-induced gradients were assessed with univariate logistic regression analysis. Values of  $P<0.05$  were considered significant. Calculations were performed with GB-STAT version 9.0 (Dynamic Microsystems, Inc, Silver Spring, Md).

## Results

### Patient Characteristics

Clinical and demographic characteristics in the study population of 320 patients are summarized in Table 1. Mean age at initial evaluation was  $47\pm 17$  years; 215 patients (67%) were male. Mean NYHA class at baseline was  $1.7\pm 0.8$ . Maximal LV wall thickness was  $22\pm 6$  mm.

### Prevalence of LV Outflow Tract Obstruction

#### At Rest

Of the 320 HCM patients, 119 (37%) had an LV outflow gradient  $\geq 50$  mm Hg at rest. The remaining 201 patients (63%) with a rest gradient  $<50$  mm Hg ( $4\pm 9$  mm Hg; range, 0 to 45 mm Hg; 0 of 178 [88%]) underwent exercise echocardiography. Patients with obstruction at rest

$\geq 50$  mm Hg (nonexercised) were older (52 versus 44 years;  $P=0.0001$ ), had greater maximal LV wall thicknesses (23 versus 21 mm;  $P=0.03$ ), and had more advanced symptoms (NYHA class 2.2 versus 1.5;  $P<0.0001$ ) than did patients who were exercised (Table 1).

#### With Exercise

For the total exercised group of 201 patients, the LV outflow tract gradient increased from  $4\pm 9$  mm Hg at rest to  $45\pm 49$  mm Hg after exercise (Figure 2). Of these exercised patients, 106 (52%) developed dynamic LV outflow gradients  $\geq 30$  mm Hg, including 76 (38%) that were particularly substantial, ie,  $\geq 50$  mm Hg. The remaining 95 patients (47%), ie, those with gradients  $<30$  mm Hg at rest and with exercise, were regarded as having the nonobstructive form of HCM (Table 2). Each of the 11 patients with rest gradients of 30 to 49 mm Hg developed gradients  $\geq 50$  mm Hg with exercise.

The 3 participating centers did not differ significantly with regard to the percentage of exercised patients who generated provokable gradients of 30 to 49,  $\geq 50$ , or  $<30$  mm Hg ( $P=0.8$ ). The 20 patients taking cardioactive medications at the time of exercise testing developed LV outflow gradients ( $\geq 30$  mm Hg) no more frequently than did the exercised patients with medications withdrawn (10 of 20 [50%] versus

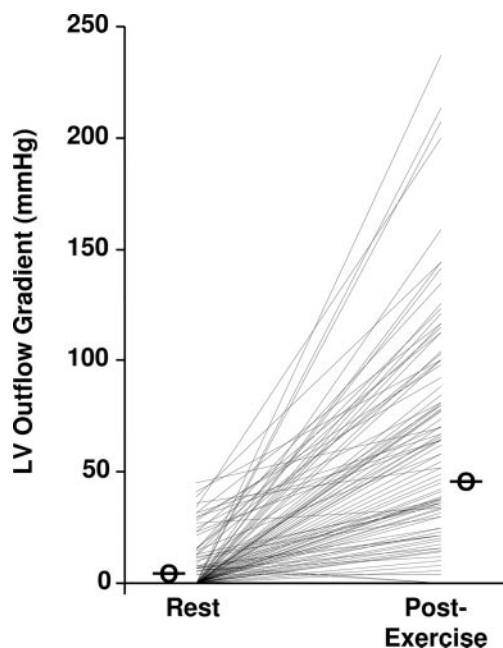
**TABLE 1. Clinical Baseline Characteristics of 320 Study Patients With HCM**

Parameter	All Patients	LVOT Gradient		<i>P</i> *
		$<50$ mm Hg at Rest (Exercised Patients)	$\geq 50$ mm Hg at Rest (Nonexercised Patients)	
Study patients, n (%)	320 (100)	201 (63)	119 (37)	NA
Age (range), y	$46.8\pm 17.0$ (13–86)	$44.0\pm 16.3$ (14–83)	$51.5\pm 17.3$ (13–86)	0.0001
Male, n (%)	215 (67)	148 (74)	67 (56)	NS
Family history of HCM, n (%)	84 (27)	60 (30)	25 (21)	NS
NYHA functional class	$1.7\pm 0.8$	$1.5\pm 0.7$	$2.2\pm 0.8$	$<0.0001$
NYHA class, n (%)				
I	151 (47)	124 (62)	27 (23)	$<0.0001$
II	97 (30)	54 (27)	43 (36)	NS
III/IV	72 (23)	23 (11)	49 (41)	$<0.0001$
Maximum LV thickness, mm	$22.0\pm 5.7$ (13–48)	$21.4\pm 5.7$ (13–48)	$22.8\pm 5.5$ (13–39)	0.03
LVOT gradient $\geq 30$ mm Hg at rest, n (%)	130 (41)	11 (5)	119 (100)	NA
LVOT gradient with exercise, mm Hg	–	$44.7\pm 49.0$ (0–237)	–	NA
Left atrium, mm	$42.8\pm 7.3$ (18–66)	$41.8\pm 6.8$ (29–63)	$44.5\pm 7.9$ (18–66)	0.005
LV end-diastolic diameter, mm	$43.4\pm 6.5$ (24–63)	$44.1\pm 6.4$ (24–63)	$42.3\pm 6.5$ (28–60)	NS
History atrial fibrillation, n (%)	45 (14)	18 (9)	27 (23)	0.003
History syncope, n (%)	37 (12)	25 (12)	12 (10)	NS
Medications, n (%)				
$\beta$ -Blocker	189 (59)	105 (52)	84 (71)	NS
Calcium channel blocker	100 (31)	46 (23)	54 (45)	0.003
Disopyramide	16 (5)	3 (2)	13 (11)	0.0004
Antiarrhythmic†	27 (8)	10 (5)	17 (14)	0.008
ACE/ARB	26 (8)	24 (12)	2 (2)	0.002
Diuretic	27 (8)	6 (3)	21 (18)	$<0.0001$

LVOT indicates LV outflow tract; ACE, angiotensin-converting enzyme inhibitor; and ARB, angiotensin receptor blocker.

\*Comparisons between exercised and nonexercised patients.

†Antiarrhythmic drugs included amiodarone, propafenone, and sotalol.



**Figure 2.** Changes in LV outflow tract gradient from basal (rest) conditions to immediately after exercise in 201 HCM patients. Each individual exercised patient is depicted by a line connecting the 2 gradient measurements.  $\ominus$  indicates mean value.

86 of 181 [47%], respectively;  $P=0.9$ ); the average exercise gradients in these 2 groups also did not differ significantly ( $31 \pm 32$  versus  $46 \pm 51$  mm Hg, respectively;  $P=0.2$ ).

Patients who generated an outflow gradient with exercise and those who were nonobstructive did not differ significantly with respect to a number of exercise testing parameters, including rate-pressure product at peak exercise<sup>30</sup> and percent maximal predicted heart rate during measurement of the postexercise gradient (Table 2). Substantial increases in mitral regurgitation from absent or mild to moderate (at baseline) to severe after exercise were evident in 14 patients (18%) with a provokable gradient  $\geq 50$  mm Hg, in 1 patient (3%) with a gradient of 30 to 49 mm Hg, and in no patient with a gradient  $< 30$  mm Hg. The average provokable gradient in the 23 patients (11%) who developed significant symptoms during exercise testing was  $63 \pm 53$  mm Hg and did not differ from that in other patients without symptoms during exercise testing ( $48 \pm 44$  mm Hg;  $P=0.1$ ).

#### Combined Patient Analysis

Overall, 225 of the 320 HCM study patients (70%) exhibited LV outflow tract obstruction at rest ( $n=119$ ) or with exercise ( $n=106$ ; Figure 3). With only exercise gradients  $\geq 50$  mm Hg included in this assessment, the overall proportion of patients with outflow obstruction was 60% ( $n=195$ ).

#### Clinical Profile and Predictors of Exercise-Induced Obstruction

Of the 106 patients who developed gradients  $\geq 30$  mm Hg with exercise, 17 (16%) had advanced heart failure symptoms (NYHA class III); 29 others (27%) had more moderate limitation (class II), and 60 (57%) were in class I (Table 2). Of the total 77 exercised patients with heart failure symptoms

(NYHA classes II and III), 46 (60%) had gradients  $\geq 30$  mm Hg ( $\geq 50$  mm Hg in 33) identified with exercise (Table 2).

Among selected clinical and echocardiographic variables (age, gender, left atrial transverse dimension, maximum LV and basal anterior septal thickness, LV end-diastolic and end-systolic cavity size, Valsalva-induced gradient and degree of SAM), only a Valsalva-induced gradient  $\geq 50$  mm Hg (hazard ratio, 24; 95% confidence interval, 2.5 to 194;  $P=0.003$ ) was an independent predictor of an exercise-induced gradient.

#### Comparison of Exercise and Valsalva Gradients

Each of 42 patients who developed an outflow gradient  $\geq 30$  mm Hg with Valsalva also provoked a gradient  $\geq 30$  mm Hg with exercise. However, of the 159 patients in whom Valsalva did not provoke a gradient, 25 (15%) developed an exercise gradient of 30 to 49 mm Hg, and 39 (25%) had an exercise gradient  $\geq 50$  mm Hg; 95 other patients (60%) were without a gradient after exercise.

Therefore, the Valsalva maneuver had a sensitivity of only 40% for identifying the presence of an exercise-induced outflow gradient. The specificity was 100% for assessing whether patients without obstruction at rest would generate a gradient with exercise (positive predictive value, 100%; negative predictive value, 60%). In patients with both a Valsalva-induced and an exercise-induced gradient, the outflow obstruction generated during the Valsalva maneuver significantly underestimated the magnitude generated during exercise. Exercise gradients exceeded Valsalva by  $24 \pm 25$  mm Hg (for the 30 to 49 mm Hg exercise-provocable group;  $P=0.04$ ) and by  $65 \pm 46$  mm Hg (for the  $\geq 50$  mm Hg exercise-provocable group;  $P<0.0001$ ; Figure 4).

#### Discussion

Since the contemporary description of HCM almost 50 years ago, LV outflow tract obstruction has been a highly visible clinical feature of this disease.<sup>1-17</sup> Recently, outflow gradients (at rest) have been shown to be independent determinants of progressive heart failure symptoms and cardiovascular mortality.<sup>13,14</sup> Patient management decisions often are predicated on the association of heart failure symptoms with the presence and magnitude of measured subaortic gradients.<sup>3,12-15,29-41</sup> Indeed, subaortic gradients in HCM may importantly affect clinical decision making in that severely symptomatic drug-refractory patients with outflow obstruction either at rest or only with physiological provocation are potential candidates for invasive septal reduction interventions (eg, surgical myectomy, or in selected cases alcohol septal ablation) to normalize LV pressures and to improve symptoms.<sup>3,6,33-43</sup>

Historically, HCM has been characterized as a predominantly nonobstructive disease, with most patients (ie,  $\approx 70\%$ ) said to demonstrate the absence of an LV outflow tract gradient under basal conditions.<sup>6,8,9,12-14,18</sup> Since the early hemodynamic studies of the 1960s,<sup>2-5</sup> a variety of pharmacological and other provocative maneuvers (eg, catecholamine-stimulating drugs such as dobutamine and isoproterenol, Valsalva maneuver, amyl nitrite inhalation, and premature ventricular contractions) have been

**TABLE 2. Demographic, Echocardiographic, and Exercise Data in 201 Patients With HCM**

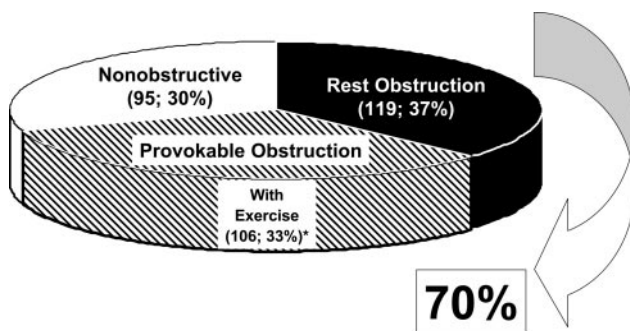
Exercise Parameter	Exercise LV Outflow Gradient, mm Hg			P*
	<30	30–49	≥50	
Patients, n (%)	95 (47)	30 (15)	76 (38)	NA
Age (range), y	43.6±16.3 (14–73)	46.8±18.8 (15–83)	43.3±15.4 (14–83)	NS
Male, n (%)	61 (64)	20 (67)	67 (88)	NS
NYHA class, n (%)				
I	64 (67)	17 (57)	43 (57)	NS
II	25 (26)	8 (27)	21 (27)	NS
III	6 (6)	5 (17)	12 (16)	NS
LVOT gradient at rest, mm Hg	0.6±1.9 (0–8)	2.8±7.2 (0–32)	8.3±13.3 (0–45)	NA
LVOT gradient with exercise, mm Hg	4.0±8.2 (0–25)	37.5±5.1 (30–49)	97.4±40.0 (50–237)	<0.0001
LVOT gradient with Valsalva ≥30 mm Hg, n (%)	0	4 (13)	13 (17)	0.0007
LVOT gradient with Valsalva ≥50 mm Hg, n (%)	0	1 (3)	24 (32)	<0.0001
LVOT gradient with Valsalva, mm Hg	0.8±3.2 (0–20)	18.4±22.6 (0–100)	32.8±33.5 (0–143)	<0.001
LA, mm	40.5±6.7 (29–62)	42.0±6.0 (33–57)	43.4±7.0 (31–63)	0.02
LVED, mm	43.8±6.4 (24–63)	43.3±6.4 (28–57)	44.6±6.4 (29–61)	NS
Maximum LV thickness, mm	21.9±5.6 (14–43)	20.8±6.4 (14–48)	21.1±5.4 (13–40)	NS
Basal septal thickness, mm	20.4±6.5 (10–43)	20.4±6.3 (10–48)	20.3±5.9 (10–40)	NS
Exercise treadmill time, min	9.40±3.32 (3–23)	9.15±3.49 (2–16.3)	10.15±3.05 (3–16.4)	NS
Peak HR, bpm	154.5±21.6 (92–196)	153.5±26.1 (100–213)	155.6±25.6 (98–205)	NS
Peak systolic BP, mm Hg	169.7±31.8 (80–238)	156.8±26.5 (100–218)	166.5±26.2 (102–220)	NS
Percent maximum HR achieved with exercise	87.6±9.9 (56–112)	90±14.7 (52–120)	87.9±11.9 (58–115)	NS
Abnormal BP response, n (%)	24 (25)	14 (47)	23 (30)	NS
Time from end of exercise to gradient measurement, s	49.7±38.3 (9–240)	48.1±33.1 (15–120)	48.6±41.8 (10–236)	NS
HR during postexercise gradient, bpm	136.4±17.2 (90–184)	133.6±21.1 (100–178)	137.1±21.0 (85–193)	NS
Percent maximum predicted HR during postexercise gradient	77.6±9.1 (54–100)	78.8±13.2 (52–103)	77.4±10.3 (56–97)	NS
Rate-pressure product at peak exercise, bpm×mm Hg	26,074±6,073 (8704±41 160)	24 084±5844 (13 000±35 150)	26 062±6073 (10 710±39 575)	NS

LVOT indicates LV outflow tract; LA, left atrium; LVED, LV end-diastolic diameter; HR, heart rate; and BP, blood pressure.

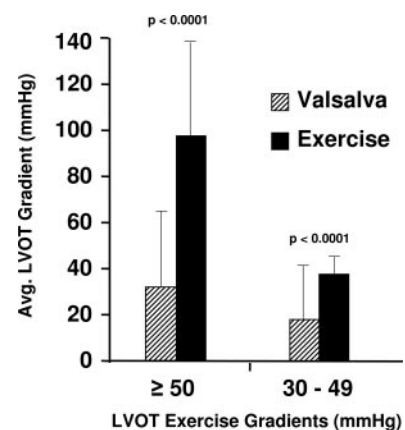
\*Comparisons (analysis of variance and  $\chi^2$  when applicable) between exercised patients in 3 subgroups classified by provokable gradient (<30, 30–49, and ≥50 mm Hg).

used in both the cardiac catheterization and echocardiography laboratories to provoke latent outflow gradients in symptomatic HCM patients with little or no evidence of obstruction at rest.<sup>2–4,12,15</sup> Nevertheless, uncertainty persists as to whether the dynamic gradients generated by such interventions can be regarded as physiological and therefore representative of those circumstances during which HCM patients develop limiting

heart failure–related symptoms while engaged in daily physical activities.<sup>6,44</sup> For those reasons, all other traditional provokable maneuvers (except Valsalva) were not incorporated into the present study design.



**Figure 3.** Prevalence of LV outflow tract obstruction in the overall study group of 320 HCM patients. \*Includes 30 patients with modest exercise gradients of 30 to 49 mm Hg and 76 patients with gradients ≥50 mm Hg.



**Figure 4.** Comparison between LV outflow tract (LVOT) gradients (≥30 mm Hg) provoked with exercise and with Valsalva maneuver. Valsalva significantly underestimates gradients vs those provoked with exercise. Avg indicates average.

The findings of this prospective cross-sectional study depart from traditional perceptions that LV outflow obstruction occurs in only a minority of HCM patients (ie,  $\approx 30\%$ ).<sup>6,8,10,13,14,19–21</sup> Conversely, we found that most HCM patients (ie,  $\approx 70\%$ ) are predisposed to LV outflow tract obstruction because of SAM-septal contact, either at rest or with physiological exercise testing. This observation holds major clinical implications for the management of HCM patients, given that subaortic obstruction is a major determinant of clinical outcome.<sup>6,13,14,31–43</sup>

In the present study, among those exercised HCM patients with no evidence of obstruction at rest,  $>50\%$  generated gradients of at least 30 mm Hg immediately after exercise, a much higher proportion than that reported by Marwick et al.<sup>16</sup> Nevertheless, the frequency and degree to which HCM patients can generate mechanical impedance to LV outflow during periods of exercise have been largely unresolved. Because exercise is the only provocative maneuver that is truly physiologically based and most relevant to conditions under which HCM patients incur symptoms, we selected upright exercise as the most appropriate and clinically applicable methodology to define the overall prevalence, clinical profile, and significance of outflow obstruction in a large, multicenter HCM cohort. Importantly, the preponderance of available evidence has demonstrated a close relationship between the magnitude of outflow obstruction elicited during exercise and in the immediate recovery period, thereby supporting the contention that subaortic obstruction measured just after cessation of exercise accurately reflects the pressure gradient generated during exercise.<sup>2,3,15,16</sup>

Of note, we also identified important subgroups of patients without gradients at rest (or with Valsalva) who nevertheless developed hemodynamically significant LV outflow obstruction only with exercise, including some with severe gradients  $\geq 50$  mm Hg. Indeed, a substantial proportion of these patients had limiting heart failure symptoms; therefore, identification of latent, exercise-triggered obstruction not only defined the probable mechanism for such symptoms but in many cases also created important options for their relief with surgical or interventional septal reduction therapies.<sup>33–43</sup> should conventional drug therapy fail. Certainly, without exercise echocardiography, the capability of such HCM patients to develop elevated LV intracavitary pressures during normal physical activity would have remained undefined. These findings are not unlike those supporting the role of exercise testing in unmasking the severity of other dynamic valvular lesions (eg, ischemic mitral regurgitation).<sup>45,46</sup>

Although the Valsalva maneuver was the only predictor of exercise-induced obstruction identified in this analysis, its low sensitivity in this regard further underscores the role of exercise echocardiography in identifying provokable obstruction. In addition, only a minority of our exercised patients with gradients developed severe mitral regurgitation, suggesting that the long-term consequences of obstruction likely are caused largely by the subaortic gradient and elevated LV pressures rather than by mitral regurgitation.

Finally, each of the 11 patients with rest gradients in the range of 30 to 49 mm Hg developed exercise-induced gradients  $\geq 50$  mm Hg. Although this subset analysis would

suggest the possibility of reducing the gradient threshold at rest for myectomy to  $\geq 30$  mm Hg, we nevertheless believe that it is most prudent for this patient subgroup to undergo stress echocardiography to directly assess the gradient response to exercise (at least until our data can be replicated in larger groups of patients). Therefore, our findings support the recommendation that all HCM patients without significant obstruction at rest undergo exercise echocardiography to assess whether physiologically provokable obstruction is present.

It should be emphasized that great care is necessary when analyzing the continuous-wave Doppler tracings in the post-exercise state. Specifically, special focus should be given to the well-recognized but often challenging circumstance of distinguishing between Doppler waveforms emanating from the LV outflow tract (indicative of subaortic obstruction typically resulting from SAM-septal contact) and the mitral regurgitation jet. Failure to accurately distinguish between these separate Doppler signals may result in overestimation of the LV outflow tract gradient (usually because of contamination by mitral regurgitation), which could ultimately lead to unnecessary septal reduction therapy.

The finding that many study patients with only exercise-provoked gradients were asymptomatic was unexpected. Although the long-term consequences of these gradients are unresolved (and beyond the scope of the present investigation), there is precedent to suggest the distinct possibility that mechanical outflow obstruction related to exercise in such patients could prove to be of pathophysiological significance over time. Support for this assertion derives from prior studies documenting the long-term deleterious effects of subaortic gradients measured in HCM patients under basal conditions<sup>6,8,10,13,14</sup> and the finding in the present cohort that most patients (ie, 60%) who developed moderate to severe heart failure symptoms did in fact generate hemodynamically significant gradients only with exercise (and often  $\geq 50$  mm Hg). However, further follow-up data relating to the natural history of exercise-provoked gradients are necessary before firm clinical recommendations can be established concerning the necessity and timing of septal reduction therapies in patients with no or mild heart failure symptoms.

The Valsalva maneuver has been a common practice for provoking outflow obstruction in HCM patients for several decades.<sup>2,4</sup> However, in the present analysis, Valsalva (compared with stress echocardiography) proved to be of very limited value in predicting exercise-provoked gradients, with a sensitivity of only 40%. Even when Valsalva-provoked gradients occurred, they consistently and significantly underestimated the magnitude of those measured after exercise. Therefore, complete reliance on the Valsalva maneuver to guide management decisions in such clinical settings could deprive some symptomatic patients of important treatment options traditionally reserved for those with LV outflow obstruction.<sup>3,6,8,31–43</sup> On the other hand, these data suggest that for those individual severely symptomatic patients unable to undergo exercise testing, the presence of a distinctly positive Valsalva maneuver alone could be sufficient to recommend invasive septal reduction therapy.<sup>38–39</sup>

The present study cohort was assembled prospectively in a consecutive fashion from 3 HCM referral centers. The prevalence of obstruction at rest (and with exercise) did not differ between the study sites or the types of upright exercise used and was similar to that previously reported from other institutions.<sup>6,8,14</sup> Nevertheless, we wish to be cautious in explicitly extrapolating our data to the general HCM population because of the patient selection bias unavoidably operative in tertiary centers and because prudent medical practice prohibited us from exercising all patients who would otherwise have been eligible for this study. Nonetheless, these data indicate that a significant proportion of HCM patients considered nonobstructive at rest will develop outflow obstruction with exercise. Whether our reported prevalence is lower (or higher) than in the general HCM population does not lessen the clear implication that the evaluation of obstruction with exercise may have important clinical implications.

### Conclusions

Mechanical obstruction to LV outflow, measured at rest and provoked with physiological exercise, was present in the majority of HCM patients in this hospital-based cohort. These observations represent an alternative perspective on the clinical spectrum of HCM, which has previously been regarded as a predominantly nonobstructive disease, and have clinical implications for the evaluation and management of symptomatic patients without basal obstruction. Indeed, only exercise echocardiography permitted these novel considerations and the identification of an important subset of HCM patients, in whom heart failure symptoms are largely explained by latent exercise-induced obstruction. Many of these patients may be (or become) candidates for major interventions such as surgical septal myectomy or alternatively alcohol septal ablation.

### Disclosures

None.

### References

1. Brock R. Functional obstruction of the left ventricle: acquired aortic subvalvular stenosis. *Guys Hosp Rep*. 1957;106:221–238.
2. Braunwald E, Lambrew T, Rockoff SD, Ross J Jr, Morrow AG. Idiopathic hypertrophic subaortic stenosis, I: a description of the disease based upon an analysis of 64 patients. *Circulation*. 1964;30(suppl IV):3–119.
3. Harrison DC, Braunwald E, Glick G, Mason DT, Chidsey CA, Ross J Jr. Effects of beta adrenergic blockade on the circulation with particular reference to observations in patients with hypertrophic subaortic stenosis. *Circulation*. 1964;29:84–98.
4. Braunwald E, Oldham HN Jr, Ross J Jr, Linhart JW, Mason DT, Fort L III. The circulatory response of patients with idiopathic hypertrophic subaortic stenosis to nitroglycerin and to the Valsalva maneuver. *Circulation*. 1964;29:422–431.
5. Ross J Jr, Braunwald E, Gault JH, Mason DT, Morrow AG. The mechanism of the intraventricular pressure gradient in idiopathic hypertrophic subaortic stenosis. *Circulation*. 1966;34:558–578.
6. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH III, Spirito P, Ten Cate FJ, Wigle ED. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Car-

- diology Committee for Practice Guidelines. *J Am Coll Cardiol*. 2003;42:1687–1713.
7. Wigle ED, EM, Rakowski P, Focsaneanu D, Sloggett C, Woo A, Rakowski H. Hypertrophic cardiomyopathy with latent (provocable) obstruction: pathophysiology and management. In: Maron BJ, ed. *Diagnosis and Management of Hypertrophic Cardiomyopathy*. Oxford, UK: Blackwell Futura Press; 2004:95–104.
8. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA*. 2002;287:1308–1320.
9. Spirito P, Seidman CE, McKenna WJ, Maron BJ. The management of hypertrophic cardiomyopathy. *N Engl J Med*. 1997;336:775–785.
10. Wigle ED, Rakowski H, Kimball BP, Williams WG. Hypertrophic cardiomyopathy: clinical spectrum and treatment. *Circulation*. 1995;92:1680–1692.
11. Klues HG, Leuner C, Kuhn H. Left ventricular outflow tract obstruction in patients with hypertrophic cardiomyopathy: increase in gradient after exercise. *J Am Coll Cardiol*. 1992;19:527–533.
12. Maron BJ, Epstein SE. Clinical significance and therapeutic implications of the left ventricular outflow tract pressure gradient in hypertrophic cardiomyopathy. *Am J Cardiol*. 1986;58:1093–1096.
13. Maron MS, Olivetto I, Betocchi S, Casey SA, Lesser JR, Losi MA, Cecchi F, Maron BJ. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med*. 2003;348:295–303.
14. Autore C, Bernabo P, Barilla CS, Bruzzi P, Spirito P. The prognostic importance of left ventricular outflow obstruction in hypertrophic cardiomyopathy varies in relation to the severity of symptoms. *J Am Coll Cardiol*. 2005;45:1076–1080.
15. Schwammenthal E, Schwartzkopff B, Block M, Johns J, Losse B, Engberding R, Borggreffe M, Breithardt G. Doppler echocardiographic assessment of the pressure gradient during bicycle ergometry in hypertrophic cardiomyopathy. *Am J Cardiol*. 1992;69:1623–1628.
16. Marwick TH, Nakatani S, Haluska B, Thomas JD, Lever HM. Provocation of latent left ventricular outflow tract gradients with amyl nitrite and exercise in hypertrophic cardiomyopathy. *Am J Cardiol*. 1995;75:805–809.
17. Criley JM. Unobstructed thinking (and terminology) is called for in the understanding and management of hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 1997;29:741–743.
18. Maron BJ, Casey SA, Poliac LC, Gohman TE, Almquist AK, Aeppli DM. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. *JAMA*. 1999;281:650–655.
19. Klues HG, Schiffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. *J Am Coll Cardiol*. 1995;26:1699–1708.
20. Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. *N Engl J Med*. 2000;342:1778–1785.
21. Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A, Mahon NG, McKenna WJ. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. *J Am Coll Cardiol*. 2000;36:2212–2218.
22. Panza JA, Petrone RK, Fananapazir L, Maron BJ. Utility of continuous wave Doppler echocardiography in the noninvasive assessment of left ventricular outflow tract pressure gradient in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 1992;19:91–99.
23. Gilbert BW, Pollick C, Adelman AG, Wigle ED. Hypertrophic cardiomyopathy: subclassification by M mode echocardiography. *Am J Cardiol*. 1980;45:861–872.
24. Shah PM, Gramiak R, Adelman AG, Wigle ED. Echocardiographic assessment of the effects of surgery and propranolol on the dynamics of outflow obstruction in hypertrophic subaortic stenosis. *Circulation*. 1972;45:516–521.
25. Sherrid MV, Chu CK, Delia E, Mogtader A, Dwyer EM Jr. An echocardiographic study of the fluid mechanics of obstruction in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 1993;22:816–825.
26. Maron BJ, Nishimura RA, Danielson GK. Pitfalls in clinical recognition and a novel operative approach for hypertrophic cardiomyopathy with severe outflow obstruction due to anomalous papillary muscle. *Circulation*. 1998;98:2505–2508.
27. Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, Froelicher VF, Leon AS, Pina IL, Rodney R, Simons-Morton DA, Williams MA, Bazzarre T. Exercise standards for testing and training: a

- statement for healthcare professionals from the American Heart Association. *Circulation*. 2001;104:1694–1740.
28. Frenneaux MP, Counihan PJ, Caforio AL, Chikamori T, McKenna WJ. Abnormal blood pressure response during exercise in hypertrophic cardiomyopathy. *Circulation*. 1990;82:1995–2002.
  29. Sadoul N, Prasad K, Elliott PM, Bannerjee S, Frenneaux MP, McKenna WJ. Prospective prognostic assessment of blood pressure response during exercise in patients with hypertrophic cardiomyopathy. *Circulation*. 1997;96:2987–2991.
  30. Gobel FL, Norstrom LA, Nelson RR, Jorgensen CR, Wang Y. The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. *Circulation*. 1978;57:549–556.
  31. Sherrid MV, Pearle G, Gunsburg DZ. Mechanism of benefit of negative inotropes in obstructive hypertrophic cardiomyopathy. *Circulation*. 1998;97:41–47.
  32. Sherrid MV, Barac I, McKenna WJ, Elliott PM, Dickie S, Chojnowska L, Casey S, Maron BJ. Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2005;45:1251–1258.
  33. Woo A, Williams WG, Choi R, Wigle ED, Rozenblyum E, Fedwick K, Siu S, Ralph-Edwards A, Rakowski H. Clinical and echocardiographic determinants of long-term survival after surgical myectomy in obstructive hypertrophic cardiomyopathy. *Circulation*. 2005;111:2033–2041.
  34. Merrill WH, Friesinger GC, Graham TP Jr, Byrd BF III, Drinkwater DC Jr, Christian KG, Bender HW Jr. Long-lasting improvement after septal myectomy for hypertrophic obstructive cardiomyopathy. *Ann Thorac Surg*. 2000;69:1732–1735.
  35. Ommen SR, Maron BJ, Olivetto I, Maron MS, Cecchi F, Betocchi S, Gersh BJ, Ackerman MJ, McCully RB, Dearani JA, Schaff HV, Danielson GK, Tajik AJ, Nishimura RA. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2005;46:470–476.
  36. Mohr R, Schaff HV, Danielson GK, Puga FJ, Pluth JR, Tajik AJ. The outcome of surgical treatment of hypertrophic obstructive cardiomyopathy: experience over 15 years. *J Thorac Cardiovasc Surg*. 1989;97:666–674.
  37. Schoendube FA KH, Keith S, Flachskampf FA, Hanrath P, Messmer BJ. Long-term clinical and echocardiographic follow-up after surgical correction of hypertrophic cardiomyopathy with extended myectomy and reconstruction of the subvalvular mitral apparatus. *Circulation*. 1995;92(suppl II):II-122–II-127.
  38. Robbins RC, Stinson EB. Long-term results of left ventricular myotomy and myectomy for obstructive hypertrophic cardiomyopathy. *J Thorac Cardiovasc Surg*. 1996;111:586–594.
  39. Morrow AG, Reitz BA, Epstein SE, Henry WL, Conkle DM, Itscoitz SB, Redwood DR. Operative treatment in hypertrophic subaortic stenosis: techniques, and the results of pre and postoperative assessments in 83 patients. *Circulation*. 1975;52:88–102.
  40. Morrow BJ, Merrill WH, Freier PA, Kent KM, Epstein SE, Morrow AG. Long-term clinical course and symptomatic status of patients after operation for hypertrophic subaortic stenosis. *Circulation*. 1978;57:1205–1213.
  41. Qin JX, Shiota T, Lever HM, Kapadia SR, Sitges M, Rubin DN, Bauer F, Greenberg NL, Agler DA, Drinko JK, Martin M, Tuzcu EM, Smedira NG, Lytle B, Thomas JD. Outcome of patients with hypertrophic obstructive cardiomyopathy after percutaneous transluminal septal myocardial ablation and septal myectomy surgery. *J Am Coll Cardiol*. 2001;38:1994–2000.
  42. Lakkis NM, Nagueh SF, Dunn JK, Killip D, Spencer WH III. Nonsurgical septal reduction therapy for hypertrophic obstructive cardiomyopathy: one-year follow-up. *J Am Coll Cardiol*. 2000;36:852–855.
  43. Gietzen FH, Leuner CJ, Obergassel L, Strunk-Mueller C, Kuhn H. Role of transcatheter ablation of septal hypertrophy in patients with hypertrophic cardiomyopathy, New York Heart Association functional class III or IV, and outflow obstruction only under provokable conditions. *Circulation*. 2002;106:454–459.
  44. Luria D, Klutstein MW, Rosenmann D, Shaheen J, Sergey S, Tzivoni D. Prevalence and significance of left ventricular outflow gradient during dobutamine echocardiography. *Eur Heart J*. 1999;20:386–392.
  45. Pierard LA, Lancellotti P. The role of ischemic mitral regurgitation in the pathogenesis of acute pulmonary edema. *N Engl J Med*. 2004;351:1627–1634.
  46. Levine RA. Dynamic mitral regurgitation: more than meets the eye. *N Engl J Med*. 2004;351:1681–1684.

### CLINICAL PERSPECTIVE

Since the first contemporary clinical description of hypertrophic cardiomyopathy (HCM) almost 50 years ago, perhaps the most visible feature of this heterogeneous disease has been mechanical obstruction to the left ventricular (LV) outflow resulting from mitral valve systolic anterior motion. Nevertheless, historically, the majority of HCM patients (almost 70%) have been characterized as nonobstructive on the basis of the absence of an LV outflow gradient at rest. Whether HCM patients have the obstructive or nonobstructive form may affect clinical decision making because those patients with severe drug-refractory symptoms and marked obstruction are candidates for septal reduction therapy, particularly surgical myectomy. In the present study, subaortic gradients were assessed prospectively in 320 consecutive HCM patients at rest and with provocation by physiological exercise (and Valsalva maneuver). The vast majority of patients (ie, 70%) had outflow obstruction (gradient  $\geq 30$  mm Hg) either at rest or with exercise. Valsalva underestimated the presence and magnitude of exercise-induced obstruction. Of 201 patients with a gradient  $< 50$  mm Hg at rest, 106 developed dynamic obstruction with exercise, including 76 who had provoked marked gradients  $\geq 50$  mm Hg and 46 with associated heart failure symptoms. These data define a new paradigm in which HCM can be regarded as a predominantly obstructive disease. LV outflow gradients, frequently associated with heart failure symptoms and often identified only with exercise, are evident in most patients (ie, 70%). Identification of LV outflow obstruction with exercise echocardiography may broaden management options in HCM by identifying symptomatic patients not otherwise regarded as potential candidates for septal reduction therapy.