Cardiopulmonary Responses and Prognosis in Hypertrophic Cardiomyopathy

A Potential Role for Comprehensive Noninvasive Hemodynamic Assessment

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ABSTRACT

OBJECTIVES This study sought to discover the key determinants of exercise capacity, maximal oxygen consumption (oxygen uptake [V_{O_2}]), and ventilatory efficiency (ventilation/carbon dioxide output [V_E/V_{CO_2}] slope) and assess the prognostic potential of metabolic exercise testing in hypertrophic cardiomyopathy (HCM).

BACKGROUND The intrinsic mechanisms leading to reduced functional tolerance in HCM are unclear.

METHODS The study sample included 156 HCM patients consecutively enrolled from January 1, 2007 to January 1, 2012 with a complete clinical assessment, including rest and stress echocardiography and cardiopulmonary exercise test (CPET) with impedance cardiography. Patients were also followed for the composite outcome of cardiac-related death, heart transplant, and functional deterioration leading to septal reduction therapy (myectomy or septal alcohol ablation).

RESULTS Abnormalities in CPET responses were frequent, with 39% ($n = 61$) of the sample showing a reduced exercise tolerance (V_{O_2} max <80% of predicted) and 19% ($n = 30$) characterized by impaired ventilatory efficiency (V_E/V_{CO_2} slope >34). The variables most strongly associated with exercise capacity (expressed in metabolic equivalents), were peak cardiac index ($r = 0.51$, $p < 0.001$), age ($r = -0.25$, $p < 0.01$), male sex ($r = 0.24$, $p = 0.02$), and indexed right ventricular end-diastolic area ($r = 0.31$, $p = 0.002$), resulting in an R^2 of 0.51, $p < 0.001$. Peak cardiac index was the main predictor of peak V_{O_2} ($r = 0.61$, $p < 0.001$). The variables most strongly related to VE/VCO2 slope were E/E′ ($r = 0.23$, $p = 0.021$) and indexed left atrial volume index (LAVI) ($r = 0.34$, $p = 0.005$) (model $R^2 = 0.15$). The composite endpoint occurred in 21 (13%) patients. In an exploratory analysis, 3 variables were independently associated with the composite outcome (mean follow-up 27 ± 11 months): peak V_{O_2} <80% of predicted (hazard ratio: 4.11; 95% confidence interval [CI]: 1.46 to 11.59; $p = 0.008$), V_E/V_{CO_2} slope >34 (hazard ratio: 3.14; 95% CI: 1.26 to 7.87; $p = 0.014$), and LAVI >40 ml/m^2 (hazard ratio: 3.32; 95% CI: 1.08 to 10.16; $p = 0.036$).

CONCLUSIONS In HCM, peak cardiac index is the main determinant of exercise capacity, but it is not significantly related to ventilatory efficiency. Peak V_{O_2}, ventilatory inefficiency, and LAVI are associated with an increased risk of major events in the short-term follow-up. (J Am Coll Cardiol HF 2015;3:408–18) © 2015 by the American College of Cardiology Foundation.

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Hypertrophic cardiomyopathy (HCM) is an inherited heart muscle disease with variable clinical expression and natural history (1). Reduced exercise capacity is common in patients with HCM, affecting patients along a broad spectrum of clinical severity (2). Several mechanisms may contribute to exercise limitation in these patients, including diastolic dysfunction, dynamic obstruction of the left ventricular outflow tract (LVOT) and left ventricular (LV) systolic dysfunction (in end-stage disease) (3,4). More recently, chronotropic incompetence has also been proposed as a potential cause of exercise intolerance in patients with HCM (5).

Cardiopulmonary exercise testing (CPET) is a reliable method to objectively evaluate exercise capacity (6). Although standard exercise testing has been available for more than a half century, modern CPET systems have evolved allowing the analysis of gas exchange at rest, during exercise, and during recovery and yield breath-by-breath measures of oxygen uptake (V_{O_2}), carbon dioxide output (V_E/V_{CO_2}), and ventilation (VE) (6,7). Noninvasive methods for quantifying cardiac output, such as bioimpedance, have recently been refined and have undergone validation for use during exercise (8,9).

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Currently the main determinant of exercise capacity in HCM patients remains an open issue. In this study we attempted to answer this question, considering morphologic (assessed with echocardiogram) and functional (assessed with CPET and impedance cardiography) features. We hypothesized that lower peak exercise cardiac index may play a significant role in driving exercise performance in this population. Our secondary aim was to probe whether patients with lower V_{O_2}, lower ventilatory efficiency, and evidence of diastolic dysfunction at rest had an increased likelihood of death, transplantation, or clinical deterioration.

METHODS

STUDY POPULATION. From a total population of 1,237 heart failure and cardiomyopathy patients consecutively referred to Stanford University between January 1, 2007 and January 1, 2012 and analyzed with CPET and impedance cardiography, we considered the subgroup of patients with HCM (consecutively enrolled, n = 156, 62% male, mean age 51 ± 14 years). In addition patients tested underwent a complete clinical assessment, including basal and exercise echocardiography. Genetic testing data from sequencing of sarcomere genes was available in 108 patients.

The diagnosis of HCM was on the basis of the presence of significant LV hypertrophy (end-diastolic wall thickness >15 mm at M-mode or 2D echocardiography) in the absence of other etiologies, according to international criteria, or wall thickness between 13 and 15 mm, in the presence of abnormal electrocardiography or familial history of inherited cardiomyopathies (2). Patients with LV systolic dysfunction were included in the study if there was a clear documented history of HCM and preserved left ventricular ejection fraction (LVEF) in previous echocardiographic examinations.

Clinical genetic testing was performed by commercial laboratories and included the sequencing of at least 8 sarcomeric genes including myosin binding protein C (*MYBPC3*), β-myosin heavy chain (*MYH7*), essential and regulatory myosin light chains (*MYL2, MYL3*), cardiac troponin T (*TNNT2*), cardiac troponin I (*TNNI3*), α-tropomyosin (*TPM1*), and cardiac actin (*ACTC*). In most cases testing also included as well as 3 genes associated with metabolic cardiomyopathies: *GLA* (for Fabry's disease), *LAMP2* (for Danon's disease), and *PRKAG2* for PRKAG2 cardiomyopathy.

The investigation aligns with the principles outlined in the Declaration of Helsinki (10), and with the local legal requirements. A written informed consent was obtained using a protocol approved by the Stanford Institutional Review Board.

ECHOCARDIOGRAPHIC AND DOPPLER STUDY. Echocardiographic images were acquired using a Philips IE 33 or HP 5500 system (Andover, Massachusetts) depending on the period of enrollment. HCM was classified according to ventricular morphology as previously described (11). Using M-mode and 2D, we measured LV diameter and fractional shortening, the thickness of the interventricular septum and LV posterior wall, and left atrial end-systolic diameter; all were measured according to the recommendations of the American Society of Echocardiography (12). Using 2D echocardiography, the sites and maximal extent of ventricular hypertrophy were assessed and measured in end-diastole. LV volumes and LVEF were assessed from the apical 4-chamber view, using the biplane method of discs (13). LVEF was considered depressed if <50%. Left atrial volumes were measured in systole just before the mitral valve opening, using a monoplane area-length method (14). At Doppler examination, systolic intraventricular gradient was quantified using the continuous-Doppler technique. A peak gradient >30 mm Hg at rest was considered significant.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CPET = cardiopulmonary exercise test

E/E' = early diastolic velocity ratio

HCM = hypertrophic cardiomyopathy

HR = heart rate

LV = left ventricular

LVEF = left ventricular ejection fraction

LVOT = left ventricular outflow tract

RV = right ventricle

V_E/V_{CO_2} = ventilation/carbon dioxide output

V_{O_2} = oxygen uptake

Mitral regurgitation severity was assessed according to American Society of Echocardiography guidelines (15). Degree of diastolic dysfunction using transmitral Doppler was classified as per previous studies (16). With tissue Doppler imaging, we considered peak myocardial early diastolic velocity measured at the lateral mitral annulus and the assessment of transmitral to tissue Doppler imaging early diastolic velocity ratio (E/E') (17). According to American Society of Echocardiography guidelines right ventricular (RV) systolic dysfunction was considered present if fractional area change (apical 4-chamber view) was <35% and/or tricuspid annular plane systolic excursion (TAPSE) was <16 mm (18).

Patients were stressed using the ramp Bruce protocol. The Borg scale (19) and the peak respiratory exchange ratio were considered as measures of adequate stress. After the treadmill exercise test patients were immediately placed in the left lateral decubitus position. Imaging was performed by an experienced technician.

CPET PROCEDURE AND DATA COLLECTION. Symptom-limited CPET was performed according to published guidelines using individualized ramp treadmill protocols (20). Ventilatory expired gas analysis was performed using CareFusion Oxycon Pro (San Diego, California) or CosMed Quark (Rome, Italy) metabolic systems. Prior to each test, the equipment was calibrated in a standard fashion using reference gases. A standard 12-lead electrocardiogram was obtained at rest, each minute during exercise, and for at least 5 min during the recovery phase; blood pressure was measured using an automated device (Suntech Tango, Morrisville, North Carolina). Minute ventilation (VE, BTPS), oxygen uptake (V_{O_2}, Standard Temperature and Pressure Dry), carbon dioxide production (VE/V_{CO_2}, STPD), and other CPET variables were acquired breath by breath, averaged over 20 s, and expressed in 10-s intervals. VE and VE/V_{CO_2} responses throughout exercise were used to calculate the VE/V_{CO_2} slope via least squares linear regression ($y = mx + b$, m = slope). Rest heart rate (HR), peak HR, ΔHR (peak HR - rest HR), and %HR reserve (HRR = ΔHR/[(220 - age) - rest HR]) were considered.

Exercise capacity was expressed as external work in metabolic equivalents (equal to treadmill speed and grade), and internal work (as peak V_{O_2}) whereas ventilator efficiency was expressed as VE/V_{CO_2} slope.

IMPEDANCE MEASUREMENTS. An impedance cardiography device (PhysioFlow model PF05 Lab1, Manatec Biomedical, Macheren, France) was used to determine stroke volume, cardiac output, and other hemodynamic variables at rest and during exercise. Details related to methods and validation of this device are available elsewhere (21). Briefly, high-frequency (75 kHz) and low-amperage (3.8 mA peak to peak) alternating electrical currents are emitted via skin electrodes (22). Two pairs of electrodes, one transmitting and the other receiving, were applied above one another so as not to overlap at the supraclavicular fossa at the left base of the neck and at the midpoint of the thoracic region of the spine. The stroke volume index calculation is dependent on the thoracic flow inversion time (m/s) measured as the first derivative of the impedance signal. The thoracic flow inversion time is the time interval between the first peak (dZ/dtmax) following the beginning of the cardiac cycle (the start of the QRS complex on the electrocardiogram) and the first zero after the nadir of the ejection velocity (dZ/dtmin) Hemodynamic variables were determined continuously at rest and during exercise and averaged over 20 s. Estimation of cardiac output was on the basis of the formula [cardiac output = HR × stroke volume index × body surface area], where cardiac output is expressed in liters per minute. Validation studies using the Physioflow device have been performed during exercise by several laboratories (22-25).

FOLLOW-UP ASSESSMENT. The combined endpoint for the study was overall mortality, heart transplantation, and functional deterioration leading to hospitalization for septal reduction (surgical myectomy or alcohol septal ablation). None of the patients had an indication for septal reduction (significant LV gradient associated with symptomatic status resistant to medical management) at enrollment. Heart transplantation indications were considered in patients in status I (refractory heart failure who required multiple hospital admissions for inotropic treatment or refractory ventricular arrhythmias, despite maximal medical and/or device therapy). Septal reduction therapy during follow-up was considered in the presence of significant heart failure symptoms associated with a significant LVOT gradient. Information concerning study endpoints was obtained directly from the computerized medical records and clinical follow-up evaluations. Follow-up was continued through May 2012.

STATISTICAL ANALYSIS. Results are expressed as mean ± SD for continuous variables or as number of cases and percent for categorical variables. Comparison of groups was performed using Student's *t* test for continuous variables with correction for unequal variance when necessary and chi-square tests or Fisher exact tests as appropriate for categorical variables. Variables that were univariately correlated with the

dependent variable were selected and entered into the multivariate model; we then performed a hierarchical procedure to optimize development of the model. A forward stepwise multiple regression analysis with a hierarchical model (considering age, sex, parameters of LV and RV dimension and systolic or diastolic function, and LV gradient) was used to determine the factors independently associated with maximal workload, V_{O_2} max, and VE/V_{CO_2} slope. We have also performed permutation testing of the significance of the p values in the multivariate models. We used 10,000 permutations to assess the significance of the variables included in the models. Permutation testing was performed in R version 3.1.1 (R Project, Vienna, Austria). A Cox proportional hazards model was used to determine factors independently associated with likelihood of death or transplantation (multivariate analysis included the variables most strongly associated with the composite outcome from univariate analysis). We used a more stringent $p < 0.01$ rather than the traditional $p < 0.05$ for significance. To determine intra- and inter-reader variability, the studies were blindly read by the same investigator as well as by a separate investigator. A random sample of 25 studies was chosen to calculate the intra- and inter-reader variability. Intra- and inter-reader variability was quantified in echocardiographic measurements using mean differences as well as intraclass correlation coefficient. For echocardiographic variables there were no significant differences in intra- and inter-reader variability (for the main variables tested p value was between 0.85 and 0.90). Statistical analysis was performed using PASW software (version 18, IBM, Chicago, Illinois).

RESULTS

STUDY SAMPLE CHARACTERISTICS. Clinical, CPET, hemodynamic, and basic echocardiographic characteristics are summarized in Table 1. The mean age of the sample was 51 ± 14 years; 96 (62%) patients were male and 22 (14%) were severely symptomatic (New York Heart Association functional class III).

Thirteen (8%) and 16 (10%) patients showed LV systolic dysfunction and a restrictive filling pattern, respectively, whereas 40 (27%) and 73 (52%) were obstructive at rest or at stress, respectively. Patients were treated mainly with beta-blockers (53%), calcium-channel blockers (24%), and angiotensin-converting enzyme inhibitors (22%). A total of 51% of the cases sent for genetic testing were genotype positive.

CARDIOPULMONARY EXERCISE TESTING. Average peak V_{O_2} was 26 ± 10 ml/kg/min; 39% (n = 61) of the cases showed reduced exercise tolerance (peak V_{O_2} <80% of predicted). The average VE/V_{CO_2} slope was 29.3 ± 6.7 and 19% (n = 30) had impaired ventilatory efficiency (VE/V_{CO_2} >34). Additionally 43%

TABLE 1 Characteristics of the Study Population at Enrollment (N = 156)

Demographic and clinical	
Age, yrs	51 ± 14
Male	96 (62)
NYHA functional class III	22 (14)
Genetic testing	
Presence of rare variant(s)*	55 (51)
Morphology	
Septal converse	12 (8)
Septal reverse	83 (53)
Apical	16 (10)
CPET responses	
Rest HR, beats/min	68 ± 13
Peak HR, beats/min	139 ± 27
% HRR (% of predicted)	68 ± 12
Rest SBP, mm Hg	118 ± 20
Peak SBP, mm Hg	222 ± 78
Peak V_{O_2}, ml/kg/min	26 ± 10
Peak V_{O_2} <80% of predict	61 (39)
VE/V_{CO_2} slope	29.3 ± 6.7
Hemodynamic responses	
Peak CI, l/min/m^2	10.1 ± 3.7
Echocardiography	
IVS, mm	17 ± 5
PW, mm	11 ± 3
LVEDD, mm	43 ± 7
LVEF, %	67 ± 11
LV systolic dysfunction	13 (8)
E'	8.3 ± 3.6
E/E'	11.8 ± 6.7
LV gradient >30 mm Hg at rest	40 (27)
LV gradient >50 mm Hg at stress	54 (35)
Restrictive pattern	16 (10)
LAVI, ml/m^2	44 ± 19
Moderate-severe MR	15 (10)
RV dysfunction	13 (8)
RVEDAI, cm^2/m^2	9.3 ± 2.3
RAVI volume, ml/m^2	24 ± 10
RVSP on 91 patients, mm Hg	29 ± 9
Therapy	
Beta-blockers	82 (53)
Calcium-channel blocker	38 (24)
ACE inhibitors	34 (22)
Diuretic agents	17 (11)

Values are mean ± SD or n (%). *On 108 genotyped patients.

ACE = angiotensin-converting enzyme; BSA = body surface area; CI = cardiac index; CPET = cardiopulmonary exercise test; E/E' = early diastolic velocity ratio; HR = heart rate; HRR = heart rate reserve; IVS = interventricular septum; LAVI = left atrial volume index; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NYHA = New York Heart Association; PW = posterior wall; RA = right atrium; RAVI = right atrial indexed volume; RV = right ventricle; RVEDAI = indexed right ventricular end-diastolic area; RVSP = right ventricle systolic pressure; VE/V_{CO_2} = ventilation/carbon dioxide output; V_{O_2} = oxygen uptake.

(n = 67) of the patients exhibited an impaired chronotropic response (<80% of predicted). Figure 1 illustrates key CPET findings.

DETERMINANTS OF EXERCISE TOLERANCE. Tables 2 and 3 summarize the associations among maximal workload, peak V_{O_2}, and VE/V_{CO_2} slope, and other clinical and echocardiographic variables using univariate and multivariate analysis. The main correlates of workload on multivariate analysis were peak cardiac index ($r = 0.51$, $p < 0.001$), age ($r = -0.25$, $p < 0.01$), male sex ($r = 0.24$, $p = 0.02$), and indexed RV end-diastolic area ($r = 0.31$, $p = 0.002$), resulting in an R^2 of 0.51 ($p < 0.001$). In the model not including hemodynamic variables, E/E' ($r = -0.21$, $p = 0.02$) was also significantly associated with workload. Figure 2 represents the relationship between peak cardiac index and maximal workload (METs).

The strongest correlates of measured peak V_{O_2} on multivariate analysis were peak cardiac index ($r = 0.61$, $p < 0.001$), age ($r = -0.32$, $p < 0.001$), male sex ($r = 0.31$, $p = 0.001$), and E/E' ($r = -0.24$, $p = 0.014$), yielding an R^2 of 0.65 ($p < 0.001$). We did not include peak HR in the model, due to the high interdependence with peak cardiac index. The model including hemodynamic variables derived with impedance cardiography had a higher coefficient of determination than the model derived with only clinical and echocardiographic parameters ($R^2 = 0.43$, $p < 0.001$). Peak cardiac index was also significantly related to peak systolic blood pressure ($r = 0.32$, $p = 0.005$).

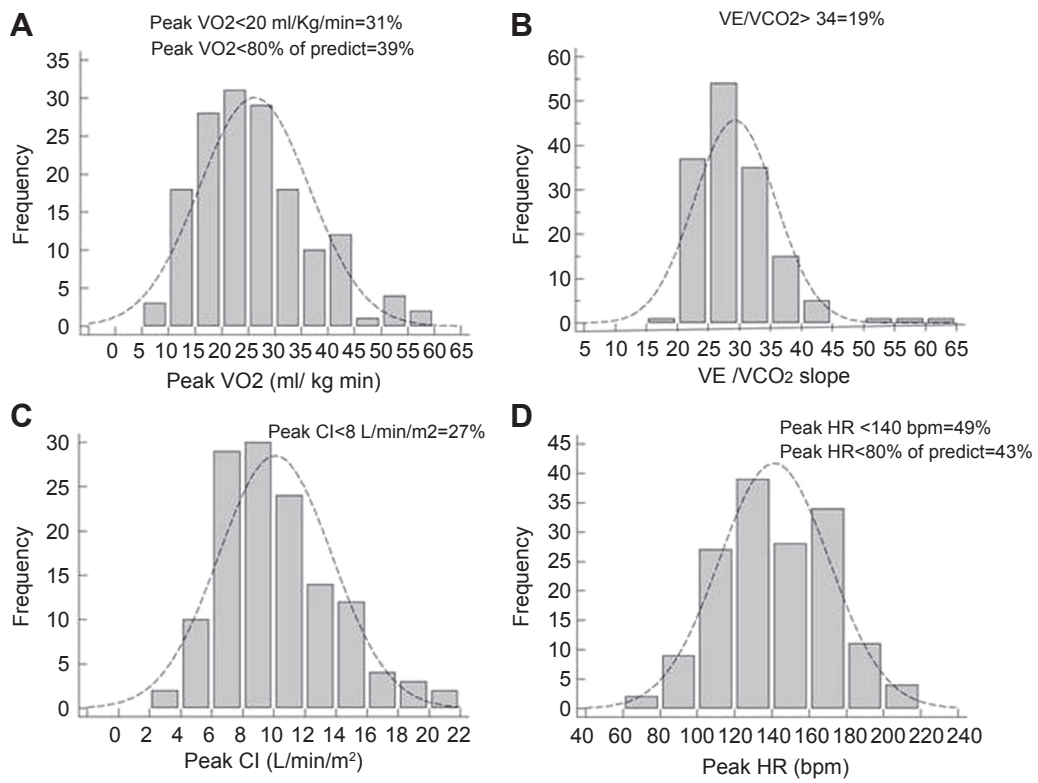
Figure 3 illustrates the variables that emerged as statistically correlated with peak V_{O_2}.

The variables most strongly associated with VE/V_{CO_2} slope were E/E' ($r = 0.23$, $p = 0.021$) and left atrial volume index ($r = 0.34$, $p = 0.005$) in the model including hemodynamic responses ($R^2 = 0.15$, $p < 0.001$).

In a model considering the genotyped patients we did not find any significant association between the presence of a disease causing variant and peak V_{O_2}, peak METs, or VE/V_{CO_2} (Figure 4).

The variables independently associated with peak cardiac index were: age ($r = 0.34$, $p < 0.001$), E/E'

FIGURE 1 Distribution of Functional and Hemodynamic Parameters in the Total Population



(A) Peak V_{O_2}, **(B)** VE/V_{CO_2} slope, **(C)** peak cardiac index (CI), and **(D)** peak heart rate (HR).

TABLE 2 Determinants of Peak Vo_2 and VE/Vco_2 in Univariate Analysis

	Univariate Peak Vo_2		Univariate VE/Vco_2	
	r	p Value	r	p Value
Demographic and clinical				
Age	-0.39	<0.001	0.19	0.21
Male	-0.30	<0.001	-0.07	0.41
NYHA functional class	-0.45	<0.001	0.13	0.09
Hemodynamic responses				
Peak HR	0.65	<0.001	-0.22	0.01
Peak CI	0.70	<0.001	-0.19	0.04
Peak SVRi	-0.55	<0.001	0.20	0.02
Echocardiography				
IVS	-0.19	0.01	0.14	0.09
PW	-0.19	0.02	0.01	0.89
LVEF	0.09	0.25	-0.03	0.68
LV gradient	-0.28	0.001	0.21	0.01
E/E'	-0.40	0.001	0.23	0.01
E'	0.44	<0.001	-0.13	0.14
S'	0.29	0.001	-0.16	0.06
LAVI	-0.21	0.009	0.38	<0.001
RVEDAI	0.34	<0.001	-0.11	0.18
TAPSE	0.24	0.003	-0.22	0.01
RVSP	-0.35	0.001	0.27	0.01

SVRi = indexed systemic vascular resistance; TAPSE = tricuspid annular plane systolic excursion; other abbreviations as in Table 1.

TABLE 3 Determinants of Peak Vo_2 and VE/Vco_2 Using Multivariate Analysis*

Peak METs (Multivariate Model)			
Impedance Variables Included (Hierarchical)		**Impedance Variables Not Included**	
R^2 = 0.51 (n = 109)	**Permutation**	**R^2 = 0.36 (n = 123)**	**Permutation**
Peak CI (r = 0.50, p < 0.001)	p < 0.001	Male (r = 0.21, p = 0.02)	p = 0.025
Male (r = 0.24, p = 0.02)	p = 0.028	Age (r = -0.35, p < 0.001)	p < 0.001
Age (r = -0.25, p = 0.01)	p = 0.029	RVEDAI (r = 0.31, p < 0.001)	p = 0.002
RVEDAI (r = 0.31, p = 0.002)	p = 0.002	E/E' (r = -0.21, p = 0.02)	p = 0.001
Peak Vo_2 (Multivariate Model)			
Impedance Variables Included (Hierarchical)		**Impedance Variables Not Included**	
R^2 = 0.65 (n = 108)	**Permutation**	**R^2 = 0.43 (n = 125)**	**Permutation**
Peak CI (r = 0.61, p < 0.001)	p < 0.001	Age (r = -0.41, p < 0.001)	p < 0.001
Male (r = 0.31, p = 0.001)	p = 0.001	Male (r = 0.22, p = 0.02)	p = 0.01
Age (r = -0.32, p < 0.001)	p < 0.001	E/E' (r = -0.22, p = 0.02)	p = 0.003
E/E' (r = -0.24, p = 0.01)	p = 0.01	LV gradient (r = -0.26, p = 0.004)	p = 0.06
		RVEDAI (r = 0.38, p < 0.001)	p < 0.001
VE/Vco_2 (Multivariate Model)			
Impedance Variables Included (Hierarchical)		**Impedance Variables Not Included**	
R^2 = 0.15 (n = 103)	**Permutation**	**R^2 = 0.16 (n = 125)**	**Permutation**
E/E' (r = 0.23, p = 0.02)	p = 0.09	E/E' (r = 0.19, p = 0.09)	p = 0.09
LAVI (r = 0.34, p = 0.005)	p < 0.001	LAVI (r = 0.36, p < 0.001)	p < 0.001

*In a model considering the 108 patients with genotype analysis the presence of mutation(s) didn't emerge significantly associated with peak METs, peak Vo_2 and VE/Vco_2.

METS = metabolic equivalents; other abbreviations as in Table 1.

(r = 0.26, p = 0.007), indexed RV end-diastolic area (r = 0.22, p < 0.03), and TAPSE (r = 0.20, p = 0.04) (R^2 = 0.34, p < 0.001).

OUTCOMES. During an average follow-up period of 27 ± 11 months, 21 (13%) patients reached the combined endpoint consisting of 4 deaths, 5 heart transplants, and 12 clinical deterioration leading to septal reduction. Patient characteristics, CPET, and hemodynamic responses in these patients who experienced an adverse event versus those who did not are shown in Table 4. Multivariate analysis identified the following variables as independently associated with the composite endpoint: peak Vo_2 <80% of predicted (hazard ratio: 4.11; 95% confidence interval [CI]: 1.46 to 11.59; p = 0.008), VE/Vco_2 slope >34 (hazard ratio: 3.14; 95% CI: 1.26 to 7.87; p = 0.014), and left atrial volume >40 ml/m^2 (hazard ratio: 3.32; 95% CI: 1.08 to 10.16; p = 0.036) (Table 5). In a model considering genotyped patients, we did not find a significant association between the presence of a known disease causing mutation and the composite endpoint. Figure 5 shows the Kaplan-Meier survival curves stratified by New York Heart Association functional class III, peak Vo_2 <80% of predicted, VE/Vco_2 <34, and left atrial volume index >40 ml/m^2.

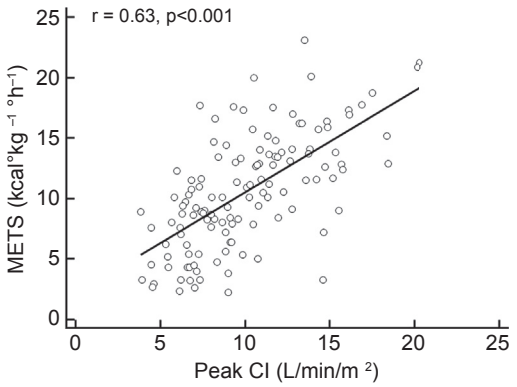
DISCUSSION

This study adds 3 contributions to an ongoing discussion on exercise intolerance and adverse events in HCM. Our data strongly suggest that peak exercise cardiac output is the primary determinant of exercise tolerance in HCM patients. Furthermore, indices of ventilatory inefficiency are only weakly associated with diastolic parameters. Finally, peak Vo_2, ventilatory inefficiency and left atrial dimension emerged as main predictors of outcome.

Previously Sharma et al. (26) studied a population of 135 HCM patients, and found that dynamic obstruction of the LVOT was associated with lower peak Vo_2, providing support for septal reduction therapy. More recently, Efthimiadis et al. (5) performed CPET in 68 patients with HCM, and found that male sex, atrial fibrillation, presence of obstruction, and HRR were independent predictors of exercise capacity. In a previous work from our group on 68 patients with HCM, Le et al. (27) reported a significant association between lateral E′ and indexed left atrial volume and peak Vo_2. The current study confirms previous reports demonstrating reduced exercise capacity in patients with HCM (in our series, 39% of the patients with reduced peak Vo_2 and 19% with significantly impaired VE/Vco_2).

Peak cardiac index emerged as the strongest independent determinant of exercise tolerance, expressed

FIGURE 2 Peak CI and Relationship With Maximal Workload (METS)

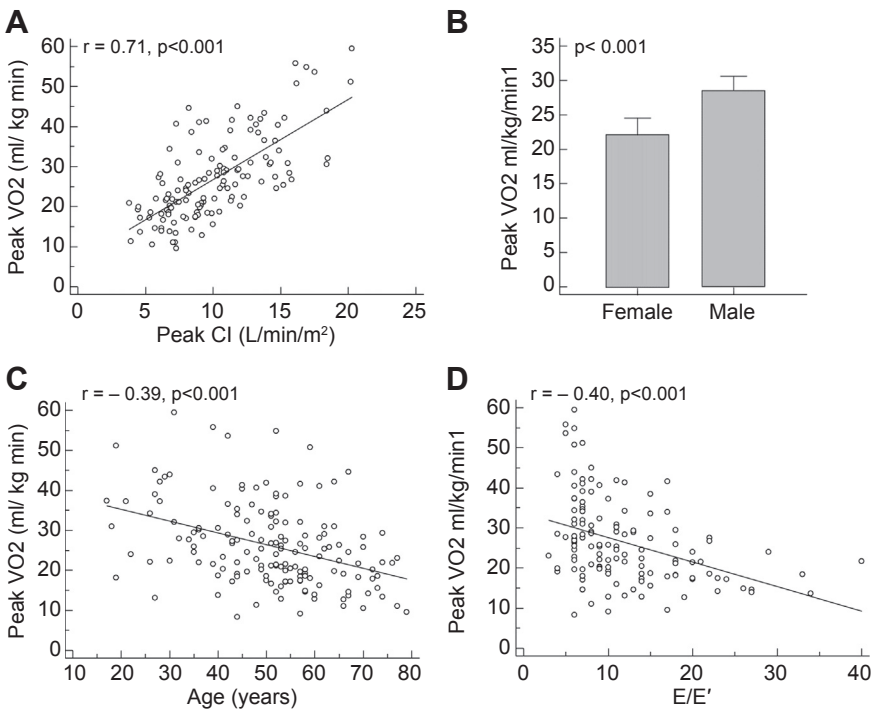


CI = cardiac index; METS = metabolic equivalents.

as either estimated METs or peak Vo_2. A linear relationship between cardiac output and peak Vo_2 has previously been demonstrated in normal subjects and in patients with heart failure (28). Frenneaux et al. (4) showed on a cohort of 23 patients with HCM studied invasively, that maximal oxygen consumption and anaerobic threshold are related to peak cardiac index, but not to peak and rest pulmonary capillary wedge pressure. Lele et al. (29) confirmed that stroke volume is the major determinant of peak exercise capacity in HCM. Given the risk and challenge of invasive hemodynamic assessment, we took advantage of the recent validation of noninvasive exercise bioimpedance. To the best of our knowledge the present study is the first to demonstrate a consistent relationship between an impaired increase in cardiac index and exercise intolerance in a large cohort of HCM patients. In agreement with previous studies, age, male sex, and diastolic parameters of the LV emerged as independent correlates of peak Vo_2 (27). Our findings underscore the importance of RV size and function in HCM. Several studies have also recently demonstrated that RV function is a key determinant of exercise capacity in heart failure with reduced systolic function (30,31).

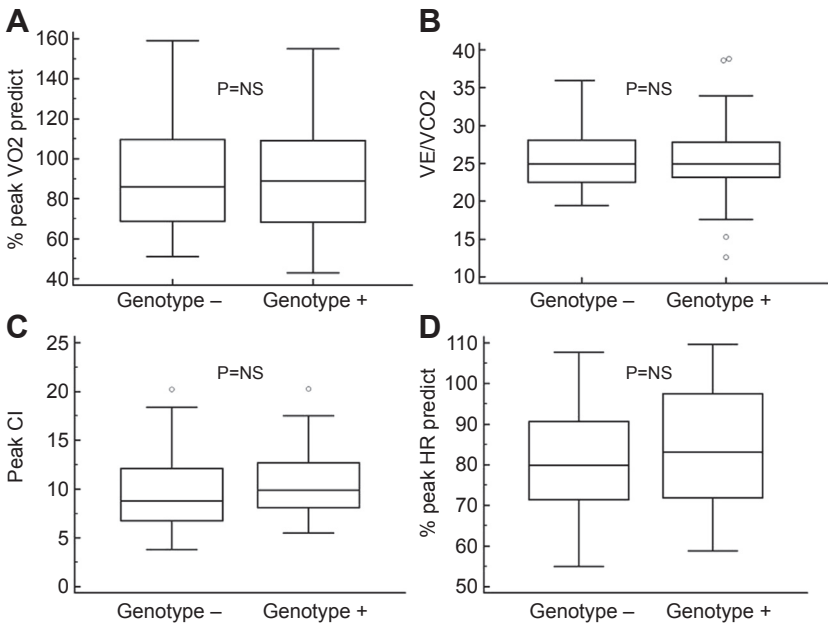
In contrast to the strong association with peak Vo_2, there was no significant association between peak cardiac index and VE/Vco_2. Ventilatory efficiency is a

FIGURE 3 Peak Vo_2 and Relationship With Clinical and Instrumental Parameters



(A) Peak cardiac index (CI), **(B)** sex, **(C)** age, and **(D)** E/E′.

FIGURE 4 Cardiopulmonary Exercise Test and Bioimpedance Values According to the Presence of Known Disease-Causing Mutation(s)



CI = cardiac index; HR = heart rate.

variable with a complex set of determinants and in systolic heart failure an abnormal VE/V_{CO_2} slope characterizes patients with more severe heart failure and is an independent marker of event free survival (14,31).

We did not find any significant relationship between CPET variables and the presence of a disease causing sarcomere variant. Efforts to characterize patients with clear sarcomeric variants and distinguish them from those without are ongoing but remain power limited.

Although our outcome evaluation was exploratory in nature, the results highlight an important prognostic role of CPET for patients with HCM. Several previous studies have considered various clinical and echocardiographic parameters in risk stratification of these patients (1,3,32). In the specific setting of HCM, studies analyzing the role of CPET variables in predicting outcomes are lacking.

Peak oxygen consumption (peak V_{O_2}) measured during a CPET has been considered a reliable variable in the assessment and risk stratification of patients with heart failure. Other variables derived from CPET have also been linked to mortality in heart failure, including peak V_{O_2} and ventilatory inefficiency expressed as the VE/V_{CO_2} slope (7,32,33). The prognostic role of CPET in HCM has never been

TABLE 4 Patient Characteristics According to the Presence of Events (Combined Event of Death, Transplantation or Need for Septal Reduction Therapy) During Follow-Up

	No Event (n = 135)	Event (n = 21)	p Value
Demographic and clinical variables			
Age, yrs	51 ± 14	51 ± 15	0.87
Sex	84 (62)	12 (57)	0.66
NYHA functional class III	15 (11)	7 (33)	0.01
Presence of mutation(s)	50 (53)	5 (38)	0.34
CPET and bioimpedance variables			
Peak HR, beats/min	141 ± 27	125 ± 26	0.03
Peak V_{O_2}, ml/kg/min	27 ± 10	18 ± 6	<0.001
Peak V_{O_2} <80% of maximum predicted	45 (33)	16 (76)	<0.001
VE/V_{CO_2} slope	28.5 ± 5.5	34.7 ± 9.9	<0.001
Peak CI, l/min/m^2	10.3 ± 3.7	8.3 ± 2.5	0.04
Peak SVRi, dyn·s/cm^5	772 ± 291	957 ± 257	0.017
Echocardiographic variables			
IVS, mm	17 ± 5	19 ± 4	0.06
PW, mm	10 ± 3	12 ± 3	0.002
LVEF, %	67 ± 9	63 ± 16	0.10
LVOT >30 mm Hg at rest	34 (26)	8 (38)	0.52
Restrictive pattern	12 (9)	4 (19)	0.19
E/E'	11 ± 7	14 ± 7	0.10
LAVI, ml/m^2	42 ± 18	55 ± 20	0.002
RVEDAI	9.2 ± 2.3	9.5 ± 1.9	0.78
TAPSE, mm	20 ± 4	20 ± 4	0.97
RVSP on 91 patients, mm Hg	28 ± 7	34 ± 12	0.018
RAVI, ml/m^2	23 ± 9	29 ± 12	0.007

Values are mean ± SD or n (%).
TAPSE = tricuspid annular plane systolic excursion; other abbreviations as in Table 1.

TABLE 5 Univariate and Multivariate Analysis of Risk of Event

	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% Confidence Interval)	p Value	Hazard Ratio (95% Confidence Interval)	p Value
Age (per 10 yrs)	1.00 (0.97-1.01)	0.83		
Male	0.85 (0.36-2.02)	0.72		
NYHA functional class III	3.39 (1.34-8.39)	0.008		
Peak HR (per 10 beats/min)	0.77 (0.74-0.79)	0.003		
Peak Vo_2 (per 5 ml/kg/min)	0.52 (0.45-0.6)	<0.001		
Peak Vo_2 <80% of predicted	5.36 (1.96-14.63)	<0.001	4.11 (1.46-11.59)	0.008
OUES	0.38 (0.20-0.74)	0.004		
VE/Vco_2 slope (per 5 U)	1.56 (1.43-1.70)	<0.001		
VE/Vco_2 slope >34	5.36 (2.21-13.01)	<0.001	3.14 (1.26-7.87)	0.014
Peak CI (per 3 U)	0.59 (0.42-0.83)	0.05		
LAVI (per 10 ml/m^2)	1.27 (1.23-1.31)	0.003		
LAVI >40 ml/m^2	3.77 (1.38-10.34)	0.001	3.32 (1.08-10.16)	0.036
RVSP (per 10 mm Hg)	1.93 (1.74-2.15)	0.01		
LV gradient at rest (per 10 mm Hg)	1.09 (0.98-1.25)	0.10		
LV gradient at stress (per 10 mm Hg)	1.11 (0.99-1.27)	0.23		
RAVI (per 5 ml/m^2)	1.52 (1.42-1.62)	0.01		

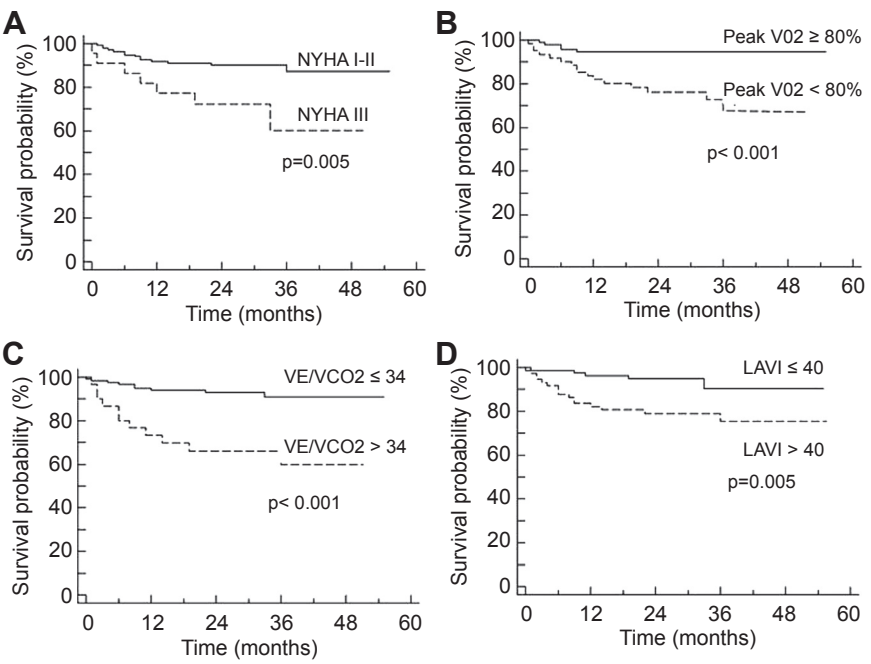
In a model considering the 108 patients with genotype analysis the presence of mutation(s) did not emerge significantly associated with the composite endpoint. Using permutation test, peak Vo_2 <80% of predicted ($p = 0.005$), VE/Vco_2 slope >34 ($p = 0.01$), and LAVI >40 ml/m^2 ($p = 0.027$).

OUES = oxygen uptake efficiency slope; other abbreviations as in Table 1.

clearly established. In a recent study Sorajja et al. (34) examined 182 minimally symptomatic patients with HCM. In a multivariate analysis, the independent predictors of death and severe symptoms were the severity of LVOT gradient at rest and the percent of predicted peak myocardial consumption during exercise. From our study both parameters of exercise tolerance (peak Vo_2 and the VE/Vco_2 slope) and indirect indices of diastolic dysfunction (left atrial volume) emerged as the main determinants of outcome. These results underscore that CPET is not limited to the general evaluation of patients or to an objective assessment of exercise tolerance, but it is also an important tool for predicting outcomes and in the general management of this disease.

STUDY LIMITATIONS. First, impedance cardiography is an indirect measure of cardiac index however the validity and reproducibility of these methods have been documented by several studies (21,24,35). Second, because of referral bias, our sample may not represent the general HCM population, as patients with more advanced disease are over-represented in specialist centers where invasive options such as

FIGURE 5 Predictors of Outcome



Event-free survival according to the presence of New York Heart Association (NYHA) functional class III at enrollment **(A)**, peak Vo_2 <80% of predicted **(B)**, VE/Vco_2 <34 **(C)**, and indexed left atrial volume index (LAVI) more than 40 ml/m^2 **(D)**.

myectomy are offered. We have however recruited consecutive patients seen in our clinic where more than 95% of patients get a baseline CPET. Finally, we chose a composite outcome, with a limited number of total events (n = 21) and a relatively short mean follow-up; thus, these findings should be viewed as preliminary.

CONCLUSIONS

Exercise intolerance is common in patients with HCM. Peak cardiac index is the main determinant of exercise tolerance, as well as other variables such as diastolic parameters, age, and sex. The failure of stroke volume augmentation during exercise seems to be influenced by age, diastolic dysfunction, and RV longitudinal dysfunction. Abnormalities in ventilatory efficiency are commonly observed in these patients and can be partially explained by the degree of diastolic dysfunction. Peak V_{O_2}, ventilatory inefficiency and parameters of diastolic function seem to be main predictors of prognosis in patients with HCM. These results remain to be validated by further multicenter studies, but they underscore an important role for CPET in the assessment of patients affected by cardiomyopathies and heart failure.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Exercise intolerance is common in hypertrophic cardiomyopathy and peak cardiac index is the main determinant of exercise capacity. Cardiopulmonary test is a helpful tool not only in diagnosis of hypertrophic cardiomyopathy but also in the prognostic assessment.

TRANSLATIONAL OUTLOOK: Further studies are warranted to determine the mechanisms underlying the reduced cardiac output during exercise in hypertrophic cardiomyopathy patients.

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