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Determinants of peak oxygen uptake in patients with hypertrophic cardiomyopathy: a single-center study

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Abstract Most patients with hypertrophic cardiomyopathy (HCM) usually complain of a reduced exercise capacity, and several factors have been advocated as possible causes of this clinical feature. The present single-center study was designed to investigate exercise capacity and its main clinical determinants in HCM patients. One hundred ninety seven patients of 223 evaluated underwent a complete clinical assessment, including Doppler echocardiography, cardiopulmonary exercise test (CPET) and, in most cases, cardiac magnetic resonance. The HCM population (male 75 %; age 47 ± 16 years; NYHA class I or II 95 %; left ventricular ejection fraction 61 ± 3 %; resting left ventricular outflow tract gradient ≥30 mmHg 22 %; late gadolinium enhancement presence 58 %) showed slightly reduced mean peak oxygen uptake values (pVO_2 75 ± 15 %, 23.2 ± 6.7 ml/kg/min) with a significant reduction of the achieved percentage of peak heart rate reserve (%pHRR 65 ± 20 %). Adopting a pVO_2 <80 % cut-off value, 59 % of HCM patients showed a reduced exercise capacity. Age, male gender, left atrial size, chronotropic and systolic blood pressure response, ventilatory efficiency, late gadolinium enhancement presence and β-blocker therapy were independently associated with pVO_2 (R^2-adjusted index 0.738). A %pHRR cut-off value of 74 % appeared to most accurately predict an impaired exercise capacity (area under curve 0.90). A great prevalence of reduced exercise capacity is present in NYHA class I–II HCM patients. Notwithstanding its multifactorial genesis, few parameters might be

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adopted in identifying this feature. In this context, %pHRR value might represent a reliable and easy-to-obtain tool for the clinical evaluation of HCM patients.

Keywords Hypertrophyc cardiomyopathy · Cardiopulmonary exercise test · Chronotropic incompetence

Introduction

Most patients with hypertrophic cardiomyopathy (HCM) report clinical symptoms such as exertional dyspnea and fatigue, resulting in decreased exercise tolerance and functional capacity [1, 2]. The pathophysiology of functional limitation in HCM is complex. Besides the occurrence of disease-related complications such as atrial fibrillation [3] or progression to end-stage phase of the disease with left ventricular (LV) remodeling and systolic dysfunction [4], several other factors have been advocated as potential causes of exercise limitation, including LV outflow tract (LVOT) obstruction [5], LV hypertrophy with myocardial fiber disarray, microvascular ischemia and interstitial fibrosis [6, 7], diastolic dysfunction, and left atrial enlargement [8–11]. Moreover, drugs commonly used in the clinical management of HCM patients, such as β-blockers and non-dihydropyridine calcium channel blockers, while exerting their beneficial effect, may contribute to effort intolerance, given their negative chronotropic effects [12]. Although previous studies have attempted to evaluate all these factors, the mechanisms of exercise intolerance in patients with HCM are not yet fully understood and remain a subject of controversy. Indeed, former investigations were performed on small HCM cohorts including patients with disease-related complications or other comorbidities known to affect exercise tolerance [8–12].

Maximal cardiopulmonary exercise test (CPET) provides an objective assessment of functional capacity in patients with HCM [13, 14], and peak oxygen uptake (pVO_2) value during exercise is a useful tool to define the presence of functional limitation and to evaluate its pathophysiological determinants. Therefore, in the present single-center cross-sectional study, CPET was performed in a large cohort of HCM patients without complications or significant comorbidities known to affect exercise capacity, with the aim of assessing the determinants of functional limitation.

Methods

Study population

We consecutively evaluated ambulatory outpatients diagnosed with HCM who were referred to the HCM Center of Azienda Ospedaliera Sant'Andrea, Sapienza University of Rome, between January 2009 and December 2011. The diagnosis of HCM was based on the two-dimensional echocardiographic demonstration of a hypertrophied, non-dilatated left ventricle (wall thickness $\geq$15 mm) in the absence of any other cardiac or systemic disease capable of producing similar magnitude of wall thickening [15].

Exclusion criteria were a history or clinical documentation of significant comorbidities, such as pulmonary embolism or valvular heart disease, pericardial disease, severe obstructive lung disease, primary pulmonary hypertension or occupational lung disease, asthma, moderate-severe renal failure (serum creatinine >2 mg/dl), and significant peripheral vascular disease. All patients with atrial fibrillation, second or higher degree atrio-ventricular block, pacemaker-dependent atrial rhythm, a previous history of alcohol-induced or surgical septal myomectomy were also excluded, as well as those with end-stage evolution, defined by dilatated LV cavity and LV ejection fraction (LVEF) <50 %. Finally, HCM patients with known coronary artery disease were also excluded from the present study analysis.

Each HCM patient who fulfilled initial inclusion criteria underwent a new complete clinical assessment, including 12-lead ECG, conventional transthoracic Doppler echocardiography, maximal symptom-limited CPET and, when possible, CMR.

All participants gave informed written consent to the procedures. The study was approved by the local internal review board and the authors had full access to and took full responsibility for the integrity of the data.

Echocardiography

All participants underwent conventional Doppler echocardiographic examination using an Acuson Sequoia® C512 (Siemens Medical Solution, CA, USA). All data were averaged on three to five measurements and were obtained according to the recommendations of the American Society of Echocardiography [16].

Conventional echocardiographic mono- and two-dimensional measurements obtained from the parasternal long axis and apical four-chamber view and reported in the present study were the following: LV end-diastolic diameter (LVEDD), maximal wall thickness (MWT, the greatest thickness measured at any site in the LV), LV mass index (LVMI = LV mass/body surface area) and left atrial volume index (LAVI = left atrial volume/body surface area). The LVEF was obtained using Simpson's biplane methods in two-dimensional echocardiography from the apical four-chamber view.

The LAVI values, the mitral inflow early filling velocity (E) to atrial filling velocity (A) ratio and the E wave

deceleration time (DT) were used for categorization of a possible LV diastolic dysfunction. Briefly, in non-obstructive HCM patients, an LAVI lower than 34 ml/m^2 was indicative of a normal filling pattern. If the LAVI was $\geq$34 ml/m^2 then the trans-mitral pulsed Doppler indexes were used to determine if "impaired relaxation" (E/A <0.8, DT >200 ms), "pseudonormal" (E/A 0.8–1.5, DT 160–200 ms) rather than a "restrictive" filling pattern (E/A >2; DT <160 ms) was present. Conversely, in those patients with LVOT gradient higher than 30 mmHg (39 patients), as well as in those without LAVI values availability (21 patients), only trans-mitral pulsed Doppler indexes together with Valsalva maneuver were interpreted [17].

Finally, in order to disclose possible dynamic LVOT obstruction, the same type of measurement was made in the orthostatic position and after a Valsalva maneuver [18].

All echocardiographic studies were executed by four physicians (E.P., B.M., L.M., G.P.) 1–7 days before CPET. Standard parasternal long and short axis of LV and apical four-chamber views were recorded with ECG and re-analyzed off-line by another expert reader (C.A.) blinded to HCM patients' identity.

Cardiopulmonary exercise test

A maximal symptom-limited CPET was performed on an electronically braked cycloergometer (Ergoline-800, Mortara, Bologna, Italy), the subject wearing a nose clip and breathing through a mass flow sensor (Quark PFT, Cosmed, Rome, Italy) connected to a saliva trap. A personalized ramp exercise protocol was performed, aiming at a test duration of 10 $\pm$ 2 min [19]. The exercise was preceded by few minutes of resting breath-by-breath gas exchange monitoring and by a 3-min unloaded warm-up. CPET was self-terminated by the subjects when they claimed that they had achieved maximal effort. A 12-lead ECG, diastolic and systolic blood pressure (SBP) were recorded during CPET, in order to obtain the following cardiovascular parameters: rest heart rate (HR), peak HR, ΔHR (peak HR $-$ rest HR), %pHR ([peak HR/(220 $-$ age)] $\times$ 100) [20], %pHR reserve (%pHRR = ΔHR/[(220 $-$ age) $-$ rest HR] $\times$ 100) [21], and ΔSBP (peak SBP $-$ rest SBP). Both rest HR and rest SBP were measured after at least 2 min with patients seated on the cycloergometer.

Predicted values for pVO_2 were calculated according to the standard formula [19]. The VO_2 versus work rate (WR) relationship was calculated as the slope of the linear relationship between VO_2 and WR from the beginning to the end of loaded exercise. Peak O_2 pulse, VO_2/HR at maximal effort, was also calculated. The anaerobic threshold was identified through a V-slope analysis of VO_2 and carbon dioxide production (VCO_2), and it was confirmed through specific behavior of O_2 (VE/VO_2) and CO_2 (VE/VCO_2) ventilatory equivalents and end-tidal pressure of O_2 and CO_2. The end of the isocapnic buffering period was identified when VE/VCO_2 increased and end-tidal pressure of CO_2 decreased. The relation between VE versus VCO_2 (VE/VCO_2 slope) was calculated as the slope of the linear relationship between VE and VCO_2 from 1 min after the beginning of loaded exercise to the end of the isocapnic buffering period [22, 23].

All CPET were executed by a single physician (D.M.) and re-analyzed by two other expert reader (F.M.C. and P.G.A.) blinded to HCM patients' clinical features.

Cardiac magnetic resonance

CMR was performed on 1.5-T MRI commercially available scanners (Sonata and Avanto, Siemens, Erlangen, Germany) within 90 days of clinical evaluation. Fast imaging with steady-state precession (FISP) sequential short-axis cine sequences (8-mm slice thickness, 2-mm gap) were acquired. Late gadolinium enhancement (LGE) images were obtained 10 min after an intravenous injection of 0.2 mmol/kg gadolinium (Gadovist, Schering, Berlin, Germany) in the same orientation as the cine images using a segmented inversion recovery sequence [24]. A cine multi-inversion time inversion recovery sequence was used to select the optimal inversion time for DE imaging. In case of incertitude or artifacts, sequences were acquired twice with different phase-encoding direction. A 90° presaturation pulse was also placed along the phase-encoding direction to eliminate ghosting.

CMR data were analyzed by two experienced observers in consensus (C.N.D.C., G.M.) blinded to clinical parameters. Ventricular volumes, LVEF and LVMI were measured from the short-axis true FISP cine images using manual segmentation on a dedicated workstation (Syngo, Siemens). A signal intensity $\geq$6 SD than the mean of normal myocardium [25] was used to define LGE areas, which were manually traced on all short-axis slices from the base to apex in the end-diastolic phase. Summing the planimetered areas yielded the total volume of LGE (g), also expressed as percentage of total LV mass.

Statistical analysis

Unless otherwise indicated, all data are expressed as mean $\pm$ SD. As a preliminary analysis, an extension of the Shapiro–Wilk test of normality has been performed. Univariate Pearson correlation was used to disclose possible correlations in the whole HCM study groups between exercise capacity and other clinical variables. For categorical variables, instead, a linear regression analysis was performed to predict the dependent variable using dummy coding, which assigns "1" and "0" to reflect the presence

and absence, respectively, of a specific category level. For instance, since three category levels are represented for NYHA in the present study, we need two dummies so that each level is uniquely defined by combining the two dummy variables. These will be the predictors (independent variables) of the regression model, where each dummy is compared to the benchmark level, coded as "0" for both dummy variables.

In order to disclose variables independently associated with exercise capacity, expressed in terms of pVO_2 (ml/kg/min), a forward–backward stepwise multivariate regression analysis was performed to provide model selection, according to the Akaike information criterion. Goodness of fit was measured by the R^2-adjusted index and by performing an analysis of residuals, where normality of these residuals is an indication of the right specification of the considered model.

Finally, a receiver-operating characteristic (ROC) analysis has been considered to determine the predictive capability of some exercise-derived parameters in identifying those patients with an impaired exercise (either on or off β-blocker treatment), expressed in terms of a pVO_2 <80 % of the maximum predicted. The behavior of a cut-off-dependent performance measure, such as accuracy, has been considered across the range of all cutoffs. Cut-off values were identified according to the accuracy [(true positive + true negative)/total sample] highest value.

Statistical analysis was performed using R (R Development Core Team, 2009) packages. All tests were two sided. A p value lower than or equal to 0.05 was considered as statistically significant.

Results

From a total of 223 patients evaluated during the study period, 197 patients met the inclusion criteria. Thirteen patients were excluded because they had echocardiographic evidence of depressed LVEF ($n = 7$) or because of a previous history of alcohol-induced or surgical septal myomectomy ($n = 6$); 8 patients because of the presence of permanent atrial fibrillation, and 5 patients were excluded because of documented history of coronary artery disease. A further 17 patients were excluded because maximal effort was not achieved (respiratory exchange ratio <1.05, $n = 14$), or because the test was interrupted for medical reasons (dizziness, $n = 2$; chest pain, $n = 1$). A total of 180 HCM patients were considered and analyzed in the actual study.

The demographic and clinical characteristics of the entire study sample are fully described in Table 1. The evaluated HCM population mainly consisted in middle-aged patients (47 ± 16 years) with a high prevalence of

Table 1 Characteristics of the entire HCM study sample ($n = 180$ patients)

Demographic	
Age, years	47 ± 16
Male, *n* (%)	134 (75 %)
BMI, kg/m^2	25 ± 4
NYHA class	
I	94 (52 %)
II	78 (43 %)
III	8 (5 %)
IV	0 (0 %)
Doppler echocardiography	
LVEDD, mm	46 ± 4
LAVI[a], ml/m^2	38 ± 11
MWT, mm	21 ± 13
LVMI, g/m^2	146 ± 46
LVEF, %	61 ± 3
LVOTO, *n* (%)	39 (22 %)
Normal filling pattern, *n* (%)	61 (34)
Impaired relaxation, *n* (%)	79 (44 %)
Pseudonormal, *n* (%)	40 (22 %)
Restrictive, *n* (%)	0 (0 %)
Cardiac magnetic resonance[b]	
LGE, *n* (%)	82 (58 %)
LV mass with LGE, %	6.5 ± 4.6
Cardiopulmonary exercise test	
Workload peak, watts	129 ± 42
pHR, bpm	137 ± 26
%pHR, % of predicted	80 ± 11
ΔHR, bpm	59 ± 19
%pHRR, % of predicted	65 ± 20
ΔSBP, mmHg	48 ± 21
pVO_2, ml/kg/min	23.2 ± 6.7
pVO_2, % of predicted	75 ± 15
pO_2 pulse, ml/beat	12.6 ± 2.9
VO_2/WR slope, ml/watt	9.5 ± 1.4
VE/VCO_2 slope	27.9 ± 5.2
RER	1.17 ± 0.08
Medications	
β-Blocker, *n* (%)	109 (61 %)
Amiodarone, *n* (%)	8 (5 %)
Verapamil, *n* (%)	9 (6 %)
ACE-i/ARBs, *n* (%)	44 (24 %)
Diuretics, *n* (%)	9 (5 %)

Data are expressed as mean ± SD or as absolute number of patients (% on total sample)

BMI Body mass index, *NYHA* New York Heart Association, *LVEDD* left ventricular end-diastolic diameter, *LAVI* left atrial volume index, *MWT* maximum wall thickness, *LVMI* LV mass index, *LVEF* LV ejection fraction, *LVOTO* LV outflow tract obstruction at rest, *LGE* late gadolinium enhancement, *pHR* peak heart rate, *ΔHR* (pHR − resting HR), *pHRR* peak HR reserve, *ΔSBP* (peak systolic blood pressure − resting SBP), *pVO$_2$* peak oxygen consumption, *pO$_2$* pulse (pVO_2/pHR), *VO$_2$/WR slope* relation between VO_2 versus work rate, *VE/VCO$_2$ slope* relation between VE versus carbon dioxide production, *RER* respiratory exchange ratio

[a] LAVI data refer only to 149 patients

[b] Cardiac magnetic resonance data refer only to 141 patients of the entire study sample

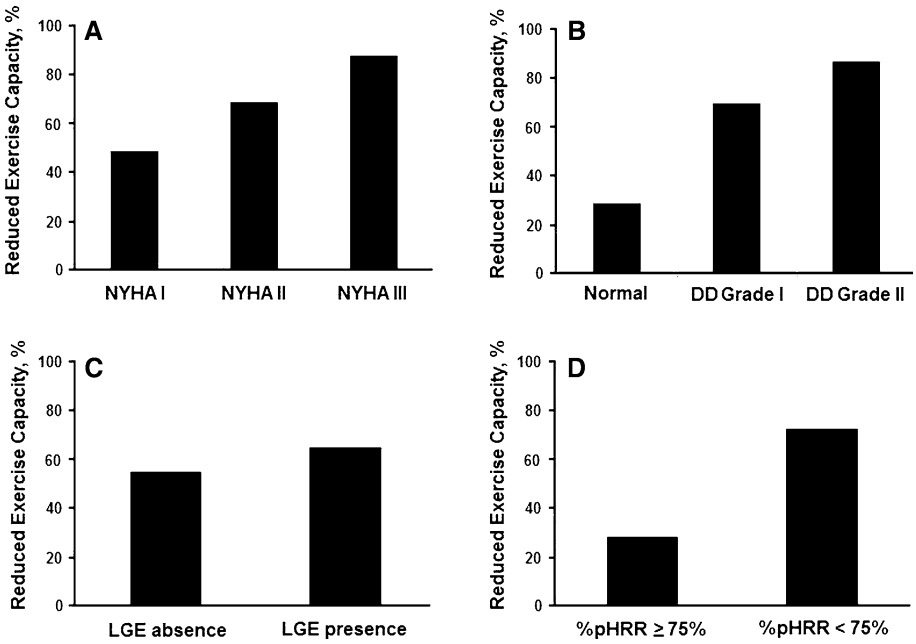

Fig. 1 Prevalence of reduced exercise (peak oxygen uptake <80 % of maximum predicted) in the entire HCM study sample according to the NYHA class (**a**), diastolic dysfunction (grade I: abnormal relaxation; grade II: pseudonormal) (**b**), late gadolinium enhancement (LGE) at cardiac magnetic resonance (**c**), and a 75 % cut-off value for predicted peak heart rate reserve (%pHRR) (**d**)

male gender (75 %) and NYHA functional class I (52 %) or II (43 %). All patients showed a preserved LVEF (61 ± 3 %), whereas the combined LAVI plus Doppler mitral flow evaluation disclosed a higher prevalence of impaired relaxation pattern (44 %) compared with normal (34 %) and pseudonormal pattern (22 %). A LVOT gradient ≥30 mmHg at rest, or after provocative maneuvers, was present in 39 patients (22 %).

A total of 141 patients (78 %) had CMR data available and fully interpretable. LGE was identified in a large percentage of this specific subgroup of patients (58 %), and it ranged from 0.4 to 23.1 % of LV mass (6.5 ± 4.6 %).

CPET revealed only slightly reduced mean pVO_2 values (23.2 ± 6.7 ml/kg/min equivalent to 75 ± 15 %), as well as peak HR (137 ± 26 bpm equivalent to 80 ± 11 %), whereas a significant reduction was observed for %pHRR values (65 ± 20 %). Within the entire HCM population, according to a pVO_2 <80 % of predicted cut-off value, 107 HCM patients (59 %) showed a reduced exercise capacity. As expected, a reduced exercise capacity was more prevalent in patients with NYHA class II (54 over 78 patients, 69 %) and NYHA III (7 over 8 patients, 88 %) with respect to those belonging to a NYHA I (46 over 94 patients, 49 %), as well it was more prevalent in those with the presence of LGE on CMR, Doppler echocardiographic evidence of impaired LV filling pressures and in those with a reduced %pHRR (Fig. 1).

One hundred nine patients (61 %) were on β-blocker therapy (42 atenolol, 9 metoprolol, and 58 bisoprolol), 44 (24 %) were receiving angiotensin converting enzyme inhibitor (ACE-i) or angiotensin receptor blocker (ARB), 9 (5 %) were taking diuretics, 9 patients (5 %) verapamil, and, finally, 8 (4 %) patients were taking amiodarone. Particularly, β-blocker therapy was administered because of the presence of LVOT obstruction ($n = 39$), and in patients complaining clinical symptoms such as dyspnea, palpitations, and/or chest pain.

Patients on β-blocker therapy were significantly older and showed higher prevalence of advanced NYHA classes, impaired LV filling and LVOT presence as well as higher values of LAVI, MWT, LVMI, and a slightly but significantly higher prevalence of LGE presence (Table 2). Most of CPET parameters and HR-derived data were also significantly lower in HCM patients with β-blockers than in the counterpart (Table 2). As expected the prevalence of reduced exercise capacity in patients taking β-blockers was higher than in those off drugs (66 vs. 49 %).

The results of Pearson correlation analysis between exercise capacity, in terms of pVO_2 (ml/kg/min), and continuous clinical variables are shown in Table 3. A significant relationship was found for age ($p < 0.000$), body mass index ($p < 0.000$), LAVI ($p < 0.000$), LVMI ($p < 0.004$), and, obviously, all CPET-derived parameters ($p < 0.001$). All categorical variables, except for verapamil and use of diuretics, were found to be significantly predictive of pVO_2 (ml/kg/min) at linear regression analysis with dummy coding (Table 3).

The forward–backward stepwise multivariate regression analysis identified the following variables as independently associated with pVO_2 (ml/kg/min): age (β −0.104; $p < 0.001$), male gender (β 2.84; $p < 0.001$), LAVI (β −0.101; $p = 0.005$), ΔHR (β 0.119; $p < 0.001$), ΔSBP (β 0.034; $p = 0.012$), VE/VCO_2 slope (β −0.196; $p = 0.002$), β-blocker therapy (β −1.49; $p = 0.045$), and

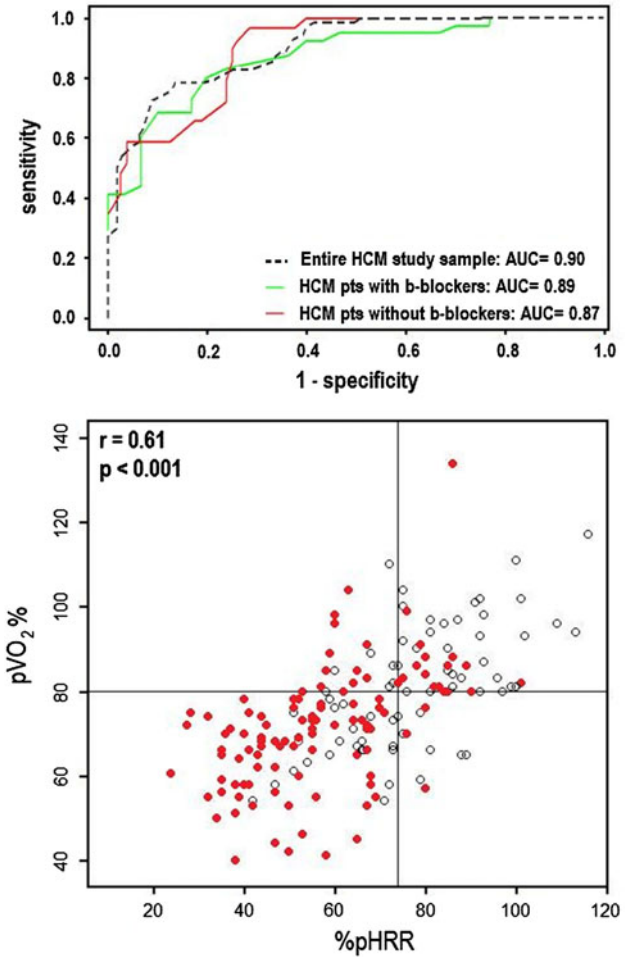

Fig. 2 *Upper panel* ROC curves comparing sensitivity and specificity of percentage of peak heart rate reserve (%pHRR) cut-off values in detecting a peak oxygen uptake (pVO_2) <80 % of maximum predicted. *Lower panel* scatter-plot of the Pearson correlation between pVO_2 and %pHRR (the *vertical line* is set at 74 % cut-off value for %pHRR and the horizontal one at 80 % pVO_2). *Filled* and *empty circles* represent patients with and without β-blocker therapy, respectively

presence of LGE (β −1.543; $p = 0.004$) (Table 3). The R^2-adjusted index for this multivariate model was 0.738.

Finally, the best exercise-derived variables able to identify with sufficient accuracy HCM patients with impaired exercise capacity (pVO_2 <80 %) are reported in Table 4. In this context, the %pHRR appeared to most accurately predict impaired exercise capacity within the entire HCM study sample with an optimal cut-off value of 74 % (sensitivity 91 %, specificity 73 %, predictive positive value 85 %, negative predictive value 84 %, AUC 0.90). Interestingly, this cut-off value did not significantly differ between HCM patients with (74 %, AUC 0.89) and without β-blocker therapy (75 %, AUC 0.87) (Fig. 2).

Table 2 Clinical and CPET data of HCM patients as per β-blocker therapy

	HCM on β-blocker ($n = 109$)	HCM off β-blocker ($n = 71$)	p values
Demographic			
Age, years	50 ± 16	42 17	0.002
Male, *n* (%)	78 (72 %)	56 (79)	Ns
BMI, kg/m^2	25 ± 4	24 ± 3	0.041
NYHA class			
I	42 (39 %)	52 (73 %)	0.000
II	60 (55 %)	18 (25 %)	0.000
III	7 (6 %)	1 (1 %)	0.000
IV	0 (0 %)	0	Ns
Doppler echocardiography			
LVEDD, mm	46 ± 4	47 ± 4	Ns
LAVI[a], ml/m^2	39 ± 11	32 ± 8	0.000
MWT, mm	21 ± 13	19 ± 5	0.05
LVMI, g/m^2	156 ± 47	131 ± 42	0.000
LVEF, %	61 ± 3	62 ± 3	Ns
LVOTO, *n* (%)	31 (28 %)	8 (11 %)	0.005
Normal filling pattern, *n* (%)	22 (20 %)	39 (55 %)	0.000
Impaired relaxation, *n* (%)	60 (55 %)	19 (27 %)	0.000
Pseudonormal, *n* (%)	27 (25 %)	13 (18 %)	0.000
Restrictive, *n* (%)	0 (0 %)	0 (0 %)	Ns
Cardiac magnetic resonance[b]			
LGE, *n* (%)	54 (49 %)	28 (39 %)	0.021
LV mass with LGE, %	6.6 ± 5.6	6.1 ± 4.1	Ns
Cardiopulmonary exercise test			
Workload peak, watts	116 ± 42	149 ± 46	0.000
pHR, bpm	126 ± 26	155 ± 21	0.000
%pHR, % of predicted	75 ± 10	88 ± 12	0.000
ΔHR, bpm	53 ± 18	69 ± 19	0.000
%pHRR, % of predicted	56 ± 17	78 ± 20	0.000
ΔSBP, mmHg	48 ± 21	52 ± 21	NS
pVO_2, ml/kg/min	20.7 ± 5.4	27.1 ± 6.7	0.000
pVO_2, % of predicted	72 ± 14	80 ± 15	0.000
pO_2 pulse, ml/beat	12.1 ± 2.9	11.8 ± 3.1	0.000
VO_2/WR slope, ml/watt	9.1 ± 1.4	9.9 ± 1.4	0.001
VE/VCO_2 slope	29.1 ± 5.1	26.1 ± 5.2	0.000
RER	1.17 ± 0.07	1.18 ± 0.07	NS
Medications			
β-blocker, *n* (%)	109 (100 %)	0 (0 %)	0.000
Amiodarone, *n* (%)	6 (5 %)	2 (3 %)	NS
Verapamil, *n* (%)	0 (0 %)	9 (12 %)	0.000
ACE-i/ARBs, *n* (%)	36 (33 %)	8 (11 %)	0.023
Diuretics, *n* (%)	7 (6 %)	2 (3 %)	0.042

Data are expressed as mean ± SD or as absolute number of patients (% on total sample). For abbreviations, see Table 1

Table 3 Significant univariate and multivariate clinical predictors of exercise capacity, as expressed in terms of pVO_2 (ml/kg/min), in the entire HCM study sample

	Univariate *r* values	*p* values	Multivariate *β* values	Multivariate SE values	*p* values
Continuous variables					
Age	−0.58	0.000	−0.104	0.023	<0.001
BMI	−0.42	0.000	–	–	–
LAVI[a]	−0.41	0.002	−0.101	0.050	0.005
LVMI	−0.23	0.004	–	–	–
Workload peak	0.84	<0.001	–	–	–
pHR	0.72	<0.001	–	–	–
%pHR	0.48	<0.001	–	–	–
ΔHR	0.77	<0.001	0.119	0.026	<0.001
%pHRR	0.56	<0.001	–	–	–
ΔSBP	0.39	<0.001	0.034	0.016	0.012
pO_2 pulse	0.53	<0.001	–	–	–
VO_2/WR slope	0.53	<0.001	–	–	–
VE/VCO_2 slope	−0.59	<0.001	−0.196	0.071	0.002
Categorical variables					
Female	Benchmark				
Male	6.6	<0.001	2.84	0.788	< 0.001
Absence of LVOTO	Benchmark		–	–	–
LVOTO	−4.7	<0.001	–	–	–
Normal filling pattern	Benchmark		–	–	–
Impaired relaxation	−7.32	<0.001	–	–	–
Pseudonormal	−6.71	<0.001	–	–	–
Absence of LGE[b]	Benchmark		–	–	–
Presence of LGE	−2.4	0.023	−1.543	0.376	0.003
Medications' free	Benchmark				
β-blocker	−6.5	<0.001	−1.491	0.605	0.045
Amiodarone	−3.5	0.047	–	–	–
ACE-i/ARBs	−3.8	<0.001	–	–	–
NYHA class I	Benchmark				
NYHA class II	−5.9	<0.001			
NYHA class III	−10.9	<0.001			

For abbreviations see Table 1

SE Standard error

[a] LAVI data refers only to 149 patients

[b] Cardiac magnetic resonance data refer only to 141 patients of the entire study sample

Discussion

Our single-center cross-sectional study, conducted in a large cohort of HCM patients on optimized treatment, shows that a considerable portion of HCM patients are affected by reduced exercise capacity. Left atrial enlargement, low chronotropic and systolic blood pressure response, increased VE/VCO_2 slope, and the presence of LGE independently predict a reduced pVO_2. Interestingly, chronotropic response seems to be a suitable exercise-derived parameter in identifying those HCM patients with reduced pVO_2 values.

We intentionally excluded from our study sample HCM patients with atrial fibrillation, end-stage progression, or other significant comorbidities known to be involved in exercise capacity reduction (i.e., coronary or peripheral artery disease) [3, 4, 26]. In spite of the above-mentioned exclusion criteria, our data highlight that a reduced exercise tolerance still affects nearly 60 % of patients in such a selected HCM population. This finding, obtained in a HCM cohort of asymptomatic or just slightly symptomatic patients, NYHA class I and II, also raises concerns about the routine clinical assessment of functional capacity in HCM patients. According to our present findings, and in line with other previous observations [13, 14], CPET should thus be taken into account [12–14, 27]. A previous analysis by Sharma and colleagues [13] in HCM patients reports a prevalence of impaired exercise capacity up to 80 %, highlighting a strong correlation between resting LVOT gradient and pVO_2. Our analysis supports the important role of LVOT obstruction in these patients, showing an independent relationship between pVO_2 and ΔSBP, the latter being strongly influenced by the development of a LVOT gradient. Indeed, the higher the exercise-induced gradient

Table 4 Variables obtained from ROC analysis in the whole HCM study sample and respective best cut-off values in identifying an impaired exercise capacity (pVO_2 <80 % of predicted)

Variables	Cut-off values	Sensitivity	Specificity	PPV	NPV	AUC
HR peak, bpm	146	79	64	78	66	0.79
%pHR, %	88	89	60	78	84	0.87
ΔHR, bpm	60	78	73	82	68	0.81
%pHRR, %	74	91	73	85	84	0.90
SBP peak, mmHg	180	73	64	73	52	0.65
ΔSBP, mmHg	50	76	74	78	56	0.70

PPV Positive predictive value, *NPV* negative predictive value, *AUC* area under the curve. For other abbreviations see Table 1

development, the lower is the exercise-induced increase in SBP. On the other hand, our slightly lower prevalence of impaired exercise capacity is likely due to the withdrawal of β-blocker therapy before CPET by Sharma et al. [13], allowing a more pronounced development of LVOT gradient during exercise [5, 17].

We found several variables significantly related to pVO_2 at univariate analysis, but only few of them remained independently associated with pVO_2 at multivariable analysis, including, besides age and gender, left atrial enlargement, low chronotropic and systolic blood pressure response to exercise, increased VE/VCO_2 slope, and presence of LGE. The multivariate-derived model was able to explain nearly the 80 % of pVO_2 changes. Several authors identify a reduced peak cardiac output as one of the leading causes of pVO_2 reduction and suggest a central role of the impaired LV diastolic filling [9–11, 28, 29]. Our data seem to support this hypothesis. Indeed, a significant LV diastolic dysfunction may be responsible for most of the variables we identified as related to a reduced exercise capacity. In fact, left atrial remodeling, known to be related to exercise capacity in non-obstructive HCM [30], has been proposed as a reliable index of chronically elevated filling pressures in patients with HCM [10, 31, 32]. Moreover, an elevated VE/VCO_2 slope value, recorded in our HCM cohort, may reflect a diastolic dysfunction and an exercise-induced ventilation/perfusion mismatch [13, 33]. Indeed, in a previous study by Arena and colleagues [33], VE/VCO_2 slope has been identified as the CPET variable with the best diagnostic accuracy for abnormal resting hemodynamics, particularly for elevated pulmonary capillary wedge pressure. This finding has been further reinforced in a recent paper from the same group, showing that in heart failure patients with preserved LVEF, ventilatory efficiency strongly correlates with E/E' ratio at tissue Doppler imaging evaluation [34].

In the present study, LGE at CMR was found in nearly 60 % of HCM patients [7, 14, 35]. In a recent investigation on patients with HCM, the extent of myocardial fibrosis, as estimated by LGE, is directly related to LV diastolic dysfunction, the latter being evaluated through assessment of LV time–volume curves [36]. Moreover, a slight but significant increase in brain natriuretic peptide values has been described in HCM patients with LGE [7, 37], again suggesting a more severe impairment of diastolic function in this setting. Thus, the significant relationship between pVO_2 and LGE in our HCM patients allows one to speculate, again, on the close dependence of exercise capacity from LV diastolic properties. The strong relationship between pVO_2 and all chronotropic parameters in our study is not surprising, as the fourfold VO_2 increase usually observed in healthy subjects during maximal effort is essentially achieved by an increase in HR [38]. Particularly, our data show that ΔHR is the variable that remains independently associated with exercise capacity in a multivariate model, and this finding overlaps with that reported in a recent paper by Efthimiadis and colleagues [14]. In patients with heart failure and preserved LVEF, as well as in those with HCM, the mechanisms involved in this phenomenon are far from being clarified. Indeed, autonomic nervous system derangement, abnormal sinus node dysfunction, and atrial fibrotic changes are all factors potentially capable of determining a reduced HR increase [38–42]. However, we may also assume that, to a certain extent, chronotropic incompetence may represent an adaptation to improve diastolic filling. Sharma and colleagues [13] report just a 15 % of chronotropic incompetence, as assessed in terms of %pHR <80 % of predicted, a prevalence significantly lower than that reported in our cohort. This apparent discrepancy could be partially due to the different criteria adopted in defining chronotropic incompetence, and to the fact that in our study, as well as in the one by Efthimiadis and colleagues [14], a large percentage of patients were on stable β-blocker therapy because of a clinical indication. This class of drug was administered to the older, sicker and most symptomatic HCM patients, thus explaining the apparent paradox of a reduced exercise capacity in HCM patients treated with β-blockers.

Finally, a remark should be reserved to %pHRR, which, among all data of cardiovascular response to exercise, demonstrates the best accuracy in detecting HCM patients with a pVO_2 lower than 80 % of predicted: Specifically, %pHRR values <75 % proved to be an index capable of identifying with an excellent sensitivity an HCM patient with reduced exercise capacity, regardless of a possible concomitant β-blocker therapy. In a real-life context where CPET is not a widespread technique, %pHRR seems to be

a simple, non-invasive tool in the functional evaluation of HCM patients, and, possibly, in therapeutic strategy management.

Limitations

Several limitations of the present study need to be acknowledged. We recognize the lack of a specific and sensible evaluation of myocardial diastolic properties through more recent Doppler techniques, such as tissue Doppler and strain imaging. This limitation does not allow us to noninvasively strengthen the primary hypothesis about a possible relationship between LV diastolic dysfunction and ΔHR in our cohort.

Another limitation of the present study is the lack of exercise stress echo data, since dynamic LVOT obstruction is reported in nearly 50 % of HCM patients [43], and it could partially account for the impaired exercise capacity. However, the occurrence of this phenomenon has been most likely reduced because of the great percentage of patients treated with β-blockers. Furthermore we classified as obstructive not only patients with a resting LVOT gradient >30 mmHg but also those with a dynamic increase of LVOT gradient over 30 mmHg after one of the most effective maneuver, such as a Valsalva [18].

This is the first study where β-blockers were not discontinued before the exercise test. Notwithstanding this methodological approach might allow a better comprehension of the real-life exercise capacity determinants in a HCM patient; however, we could not ascertain the real influence of β-blockers therapy on exercise capacity. Indeed, we are strongly convinced that this class of drug does not reduce ΔHR as has been reported in HF patients [12], this hypothesis requires being tested in a specifically trained study.

Conclusions

In conclusion, our single-center study highlights an important prevalence of reduced exercise capacity also in NYHA class I and II HCM patients on optimized treatment, and it indirectly suggests diastolic dysfunction as its leading cause. Chronotropic reserve, as assessed by %pHRR value, may be a reliable marker of reduced pVO_2 and provide a useful support in the evaluation of functional capacity of HCM patients for cardiologists operating in centers where CPET is not available.

Conflict of interest None.

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