Exercise oxygen pulse kinetics in patients with hypertrophic cardiomyopathy

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2021-320569).

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ABSTRACT

Objectives Reduced cardiac output (CO) has been considered crucial in symptoms' genesis in hypertrophic cardiomyopathy (HCM). Absolute value and temporal behaviour of O_2-pulse (oxygen uptake/heart rate (VO_2/HR)), and the VO_2/work relationship during exercise reflect closely stroke volume (SV) and CO changes, respectively. We hypothesise that adding O_2-pulse absolute value and kinetics, and VO_2/work relationship to standard cardiopulmonary exercise testing (CPET) could help identify more exercise-limited patients with HCM.

Methods CPETs were performed in 3 HCM dedicated clinical units. We retrospectively enrolled non-end-stage consecutive patients with HCM, grouped according to left ventricle outflow tract obstruction (LVOTO) at rest or during Valsalva manoeuvre (72% of patients with LVOTO <30; 10% between 30 and 49 and 18% ≥50 mm Hg). We evaluated the CPET response in HCM focusing on parameters strongly associated with SV and CO, such as O_2-pulse and VO_2, respectively, considering their absolute values and temporal behaviour during exercise.

Results We included 312 patients (70% males, age 49±18 years). Peak VO_2 (percentage of predicted), O_2-pulse and ventilation to carbon dioxide production (VE/VCO_2) slope did not change across LVOTO groups. Ninety-six (31%) patients with HCM presented an abnormal O_2-pulse temporal behaviour, irrespective of LVOTO values. These patients showed lower peak systolic pressure, workload (106±45 vs 130±49 W), VO_2 (21.3±6.6 vs 24.1±7.7 mL/min/kg; 74%±17% vs 80%±20%) and O_2-pulse (12 (9–14) vs 14 (11–17) mL/beat), with higher VE/VCO_2 slope (28 (25–31) vs 27 (24–31)) (p<0.005 for all). Only 2 patients had an abnormal VO_2/work slope.

Conclusion None of the frequently used CPET parameters, either as absolute values or dynamic relationships, were associated with LVOTO. Differently, an abnormal temporal behaviour of O_2-pulse during exercise, which is strongly related to inadequate SV increase, correlates with reduced functional capacity (peak and anaerobic threshold VO_2 and workload) and increased VE/VCO_2 slope, identifying more advanced disease irrespectively of LVOTO.

INTRODUCTION

Fatigue and dyspnoea leading to a reduced exercise performance are common symptoms in patients affected by hypertrophic cardiomyopathy (HCM).[1 2] Several are the possible mechanisms of these clinical features, such as left ventricle outflow tract (LVOT) obstruction, diastolic dysfunction, chronotropic incompetence, mitral regurgitation (MR), supraventricular arrhythmias (mostly atrial fibrillation) or progressive heart failure due to left ventricle (LV) remodelling and systolic dysfunction.[3–5] Regardless of the underlying mechanism, a reduced forward cardiac output (CO) has been considered crucial for these symptoms' genesis.

In patients with HCM, maximal cardiopulmonary exercise test (CPET) provides an objective assessment of functional capacity, as well as prognosis.[6–8] Specifically, peak oxygen uptake (VO_2) and ventilation (VE) versus carbon dioxide production (VE/VCO_2) relationship slope emerged as key prognostic variables in patients with HCM.[7 9] Of note, among CPET parameters, VO_2, both at peak and at anaerobic threshold, and O_2-pulse (VO_2/heart rate) are those more strictly related to stroke volume (SV) and CO. However, more than the absolute values, the temporal behaviour of O_2-pulse and VO_2/work relationship during exercise closely reflect SV and CO changes, respectively. Despite the evidence of the prognostic and clinical relevance of peak VO_2 and VE/VCO_2 slope,[7] no previous studies have been focused on O_2-pulse exercise-induced changes in patients with HCM. Knowing the kinetics of VO_2 and O_2-pulse during exercise may lead to a better understanding of the pathophysiological basis of the impaired exercise tolerance in patients with HCM with and without LVOT obstruction.

The purpose of the present study was to evaluate the cardiopulmonary response to exercise in patients with HCM, according to the degree of LVOT obstruction, focusing on CPET parameters strongly associated with SV and CO, both as absolute values (at anaerobic threshold and peak exercise), and—most importantly—as their exercise induced progressive changes (O_2-pulse/work and VO_2/work relationship, respectively).

METHODS

Study population and inclusion/exclusion criteria

We retrospectively enrolled all consecutive patients with a previous diagnosis of HCM, on optimised medical therapy, performing CPET

at three cardiopulmonary exercise test laboratories between January 2009 and October 2020. HCM was defined as a wall thickness ≥15 mm in one or more LV myocardial segments, as measured by any imaging technique (echocardiography, cardiac MRI or CT), which is not explained solely by loading conditions. The clinical diagnosis of HCM in first-degree relatives of patients with unequivocal disease (wall thickness ≥15 mm) was based on the presence of otherwise unexplained increased LV wall thickness ≥13 mm in one or more LV myocardial segments.[10]

Exclusion criteria were the use of long-term oxygen therapy, the presence of comorbidities affecting the possibility to perform CPET or interfering with exercise performance and concomitant at least moderate chronic obstructive pulmonary disease.

LVOT obstruction was defined as a peak instantaneous Doppler LV outflow tract gradient of ≥30 mm Hg. Since, according to guidelines,[10] the threshold for invasive treatment was usually considered to be ≥50 mm Hg despite optimal medical therapy, we used these gradient cutoffs (30 and 50 mm Hg) to divide our population in three subgroups: LVOT maximum gradient <30 mm Hg, between 30 and 50 mm Hg and ≥50 mm Hg, measured at rest or during Valsalva manoeuvre.

Cardiopulmonary exercise test

All CPETs were performed by means of a stationary ergospirometer (Quark PFT Cosmed or 229D Spectra metabolic cart, SensorMedics) using an electronically braked cycle ergometer. CPETs were interpreted by expert physicians daily involved in cardiopulmonary exercise evaluation. All subjects had previously experienced CPET in our laboratories and were in stable clinical condition at the time of enrolment, with no clinical events in the previous 6 months. The progressively increasing workload exercise protocol (ramp) was set to achieve peak exercise in ~10 min.[11] We performed breath-by-breath analysis of expiratory gases and VE. Predicted values for peak VO_2 were calculated according to Hansen *et al*.[12] The respiratory exchange ratio (RER) was measured as VCO_2/VO_2. The VO_2/work rate relationship was calculated as the slope of the linear relationship between VO_2 and work rate from the beginning to the end of loaded exercise and its abnormality was defined as a slope reduction according to Belardinelli *et al*.[13] Peak O_2-pulse, defined as VO_2/heart rate at maximal effort, was also calculated. The behaviour of the O_2-pulse during effort was assessed analysing the shape of the O_2-pulse/work relationship by visual inspection as continuously up-sloping (figure 1A), late flattening (figure 1B), early flattening (figure 1C) or down-sloping during the exercise (figure 1D). The flattening of the O_2-pulse/work relationship before the final third (<65%) of the exercise was defined as early, while the O_2-pulse/work relationship turn down in the terminal phase of the exercise was defined as down-sloping. Early flattening (figure 1C) or down-sloping (figure 1D) of the O_2-pulse/work relationship were considered as abnormal and suggestive of SV reduction during exercise

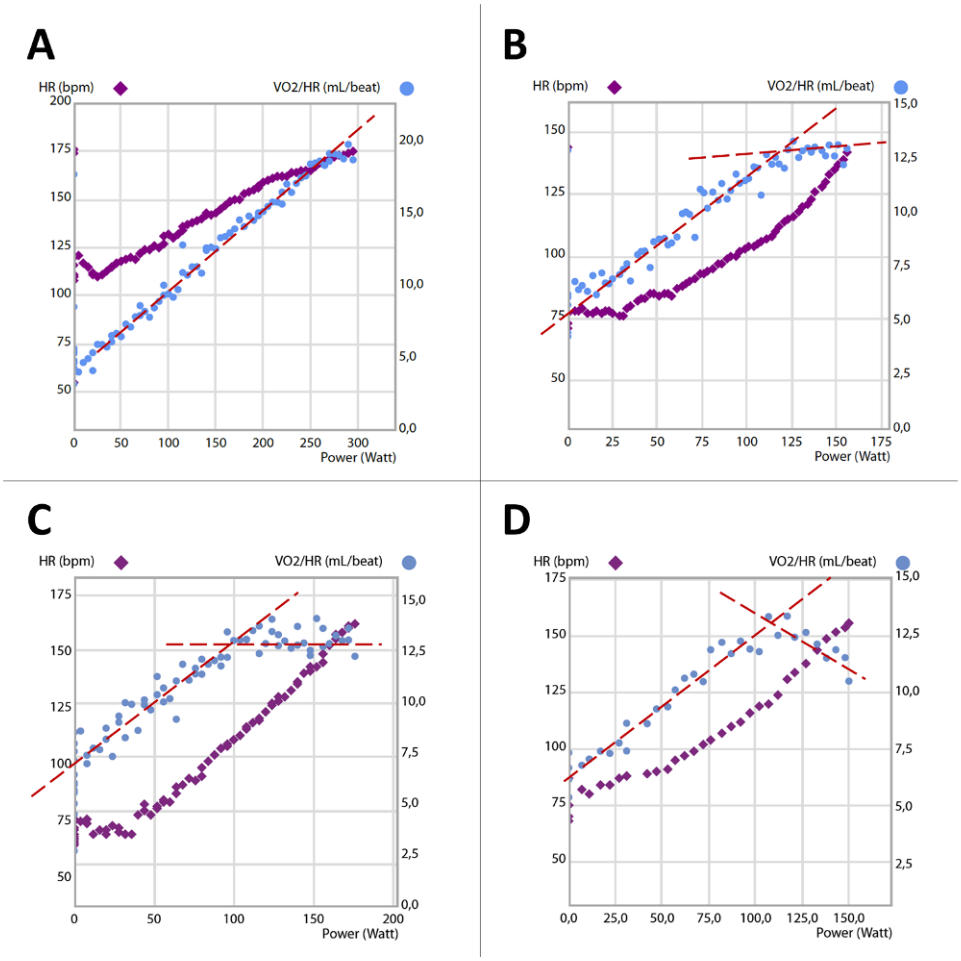

Figure 1 Behaviours of O_2-pulse kinetic. Different O_2-pulse kinetics during exercise with: a constant increase during the whole exercise (panel A), a physiological flattening at the end of exercise (panel B), an 'early flattening' pattern (panel C) and a 'down-sloping' behaviour (panel D). The latter two pictures are considered suggestive of an abrupt stroke volume reduction during the effort. The red dashed lines indicate the O_2-pulse trend.

(figure 1). To this task, a computerised graphical analysis was a helpful tool.

Standard criteria were used to identify the anaerobic threshold and VE/VCO_2 slope.[14] Finally, the breathing reserve was calculated from the standard following equation: breathing reserve (%)=100×(maximal voluntary ventilation−peak minute VE)/maximal voluntary ventilation.[15]

Statistical analysis

We estimated a sample size of 300 subjects to assess as significant (alpha=0.0167, in accordance with Bonferroni's adjustment) a mean difference in VO_2 of 6 mL/kg/min between the three groups, assuming an SD of 15 mL/kg/min and a statistical power of 80%.

Variables were expressed as mean and SD, median and IQR or counts and percentage, as appropriate. The analysis of variance test or the Brown-Forsythe test were calculated in order to compare mean values of normally distributed continuous parameters across groups according to the presence or absence of variance in homogeneity; post hoc comparisons were calculated by using the Bonferroni or Tamhane correction, respectively. For non-Gaussian continuous parameters, comparisons were made by the Kruskal-Wallis. The χ^2 test or the Fisher's exact test were calculated for discrete variables. A p value of <0.05 was considered statistically significant. Statistical analyses were performed in IBM SPSS Statistics 25 (IBM, Armonk, New York, USA).

Patient and public involvement statement

For the retrospective nature of the study, patients and public were not involved in the research protocol writing.

RESULTS

Study population characteristics

Three hundred and nineteen patients with a diagnosis of HCM were enrolled in the study. Seven patients were excluded because of presenting with an end-stage form of the disease, defined as an LV ejection fraction (LVEF) ≤35%. Among the remaining 312 patients, no patient had exercise-induced oscillatory breathing, 224 (72%) presented a non-obstructive disease, defined as an LVOT gradient <30 mm Hg at rest or during Valsalva manoeuvre. Instead, 88 (28%) patients had an obstructive disease: in 32 out of 88 (36%) the maximum gradient was between 30 and 49 mm Hg, while 56 (64%) presented a gradient ≥50 mm Hg.

The clinical and demographic characteristics of the study population are summarised in table 1. Patients with a higher gradient were older, with higher LVEF, greater wall hypertrophy and more frequently presented moderate or severe MR at rest echocardiography. Finally, β-blockers and calcium channel blockers were more frequently prescribed to patients with obstructive HCM, particularly those with LVOT gradient ≥50 mm Hg (table 1, online supplemental table S1).

Cardiopulmonary test results

Table 2 shows the main CPET results according to LVOT gradient. On average, CPETs were maximal from a metabolic point of view (peak RER ≥1.05) in all classes of patients. Patients with obstructive HCM reached a lower peak heart rate and a lower Watt value at peak exercise than subjects with non-obstructive HCM, probably resulting from a more frequent prescription of β-blockers and calcium channel blockers. Peak VO_2, measured as mL/kg/min, progressively decreased in parallel with increasing LVOT gradient however, due to age differences, no significant changes were observed when reporting peak VO_2 data as a per cent of predicted. Likewise, peak O_2-pulse was in the normal range regardless of LVOT gradient and similar among HCM groups. Moreover, VE/VCO_2 slope did not differ between HCM groups.

An abnormal O_2-pulse behaviour during exercise was observed in approximately one-third of the patients with HCM (96 out of 312), with no significant differences among LVOT groups (table 2, online supplemental table S2). Of note, the presence of an abnormal O_2-pulse behaviour was not linked to LVOT gradient at rest or during Valsalva manoeuvre. Finally, only two patients, one with obstructive HCM and one without, had an abnormal VO_2/work slope.

Table 3 shows CPET results divided according to O_2-pulse kinetic. Patients with an abnormal O_2-pulse kinetic (n=96) had a lower peak systolic blood pressure and a more compromised exercise performance, as shown by lower peak workload, peak VO_2 and O_2-pulse, while VE/VCO_2 slope was slightly higher. Similarly, the anaerobic threshold was reached at a lower VO_2 in patients with an abnormal O_2-pulse kinetic behaviour. Instead, there was no statistically significant difference in VO_2/work between the two groups.

The main findings of our study are graphically summarised in figure 2.

DISCUSSION

The present study is the first to evaluate the behaviour of O_2-pulse during exercise, that is, a non-invasive surrogate of SV changes, in patients with HCM. Assessing a multicentre cohort of 312 consecutive outpatients with HCM, we demonstrated that only the O_2-pulse kinetic during exercise identifies subjects with HCM with the most compromised exercise performance. Moreover, the presence of a low VO_2 at peak and anaerobic threshold, a low peak exercise O_2-pulse or an abnormal O_2-pulse

Table 1 Clinical and demographic characteristics of the study population

	Overall population, n=312	LVOT gradient <30 mm Hg, n=224	LVOT gradient 30–49 mm Hg, n=32	Gradient ≥50 mm Hg, n=56	P value
Age (years)	49±18	48±18	51±18	54±16	0.054
Male (n)	70% (217)	70% (157)	69% (22)	68% (38)	0.944
BMI (kg/m^2)	26.0±4.2	25.7±4.3	26.0±3.6	26.6±4.1	0.354
LVEF (%)	65 (60–65)	60 (60–65)	65 (62–68)	65 (60–65)	0.044*
Max wall thickness (mm)	19 (17–22)	19 (16–22)	22 (19–24)	20 (17–23)	0.023*
MR moderate-to-severe (n)	9.1% (28)	5.5% (12)	3.1% (1)	26.8% (15)	<0.0001†
βB or CA (n)	70% (219)	65% (146)	71% (23)	89% (50)	0.002†

*Gradient <30 vs gradient 30–49.
†Gradient <30 vs gradient ≥50.
BMI, body mass index; CA, calcium channel blockers; LVEF, left ventricle ejection fraction; LVOT, left ventricle outflow tract; MR, mitral regurgitation; βB, beta-blockers.

Table 2 Cardiopulmonary test results divided according to LVOT gradient

	Overall population, n=312	LVOT gradient <30 mm Hg, n=224	LVOT gradient 30–49 mm Hg, n=32	Gradient ≥50 mm Hg, n=56	P value
Peak workload (W)	122±49	126±51	112±46	111±40	0.053
AT workload (W)	65±29	66±30	64±30	63±28	0.777
Peak RER	1.13±0.08	1.13±0.09	1.12±0.07	1.12±0.08	0.937
Peak HR (beats/min)	133±28	137±28	127±28	125±24	0.006*
AT HR (beats/min)	100±20[a]	102±20[b]	98±21[c]	95±17[d]	0.060
Peak SBP (mm Hg)	165±30	164±29	165±29	169±31	0.469
Peak DBP (mm Hg)	88±12	88±12	86±13	89±12	0.459
Peak VE (L/min)	65±21	66±21	60±21	61±20	0.085
Peak VO_2 (mL/min)	1743±620	1789±650	1630±579	1621±489	0.107
Peak VO_2 (mL/kg/min)	23.1±7.5	24.0±8.1	21.2±6.1	20.8±4.8	<0.0001*
Peak VO_2 (% of predicted)	78±19	79±20	72±16	76±17	0.158
VE/VCO_2 slope	28 (25–32)	28 (24–31)	27 (24–32)	27 (25–30)	0.799
AT VO_2 (mL/min)	1122±353	1139±363	1085±345	1073±314	0.403
AT VO_2 (mL/kg/min)	14.8±4.4	15.2±4.8	14.1±3.5	13.5±3.2	0.007
AT VO_2 (% VO_2 max predicted)	62 (57–68)	61 (56–68)	62 (59–69)	64 (59–68)	0.701
O_2-pulse peak (mL/beat)	12.9 (10.4–15.6)	13.1 (10.7–16.2)	12.0 (9.9–17.7)	12.5 (11.0–15.1)	0.693
O_2-pulse peak (% of predicted)	103±24	102±24	102±23	107±23	0.398
VO_2/Work slope	10.8 (9.7–12.0)	10.9 (9.9–12.2)	11.0 (9.4–12.1)	11.2 (9.9–12.3)	0.657
Breathing reserve (%)	49 (38–58)	49 (36–58)	48 (37–59)	53 (42–56)	0.761
Abnormal O_2-pulse (n)	31% (96)	32% (72)	38% (12)	21% (12)	0.224

Anaerobic threshold was identified in: a. 301 out of 312 cases; b. 216 out of 224 cases; c. 31 out of 32 cases; d. 54 out of 56 cases.
*Gradient <30 vs gradient ≥50.
AT, anaerobic threshold; DBP, diastolic blood pressure; HR, heart rate; LVOT, left ventricle outflow tract; RER, respiratory exchange ratio; VE/VCO_2 slope, relation between VE versus carbon dioxide production; SPB, systolic blood pressure; VE, ventilation; VO_2, oxygen uptake.

kinetic or VO_2/work relationship, were independent from LVOT gradient value at rest or during Valsalva manoeuvre.

Indeed, the major pathophysiological mechanisms supposedly leading to a poor exercise tolerance in patients with HCM are a blunted exercise CO increase, attributable to a decrease in SV growth, and, to a lesser extent, the presence of chronotropic incompetence.[16 17] Two are the CPET parameters directly associated with a low CO and SV:VO_2, both at peak exercise and

Table 3 Cardiopulmonary test results, pharmacological therapy and moderate-to-severe MR occurrence according to O_2-pulse slope characteristic

	Normal O_2-pulse kinetic, n=211*	Abnormal O_2-pulse kinetic, n=96*	P value
Age (years)	49±18	49±18	0.929
Peak workload (W)	130±49	106±45	<0.0001
Peak RER	1.12±0.08	1.14±0.09	0.011
Peak HR (beats/min)	133±28	135±28	0.482
Peak SBP (mm Hg)	168±28	158±32	0.012
Peak DBP (mm Hg)	88±12	88±13	0.925
Peak VE (L/min)	67±21	61±22	0.018
Peak VO_2 (mL/min)	1848±621	1533±567	<0.0001
Peak VO_2 (mL/kg/min)	24.1±7.7	21.3±6.6	0.002
Peak VO_2 (% of predicted)	80±20	74±17	0.013
VE/VCO_2 slope	27 (24–31)	28 (25–31)	0.036
AT VO_2 (mL/min)	1144 (898–1362)[a]	953 (774–1287)[b]	0.002
AT VO_2 (mL/kg/min)	14.9 (11.9–17.7)	13.8 (11.5–16.0)	0.066
AT VO_2 (% of VO_2 max predicted)	61 (56–66)	64 (59–73)	0.018
O_2-pulse peak (mL/beat)	14 (11–17)	12 (9–14)	<0.0001
O_2-pulse peak (% of predicted)	106±25	98±23	0.005
VO_2/Work slope	11.1 (10.3–12.3)	10.6 (9.2–11.8)	0.103
Breathing reserve (%)	49 (38–57)	51 (35–58)	0.380
βB or CA (n)	68% (143)	76% (73)	0.141
MR moderate-to-severe (n)	7.7% (16)	10.5% (10)	0.414

Anaerobic threshold was identified in: a. 201 out of 211 cases; b. 88 out of 96 cases.
*In five patients, HR recording at peak exercise was unreliable.
AT, anaerobic threshold; CA, calcium channel blockers; DBP, diastolic blood pressure; HR, heart rate; LVOT, left ventricle outflow tract; MR, mitral regurgitation; RER, respiratory exchange ratio; VE/VCO_2 slope, relation between VE versus carbon dioxide production; SPB, systolic blood pressure; VE, ventilation; VO_2, oxygen uptake; βB, beta-blockers.

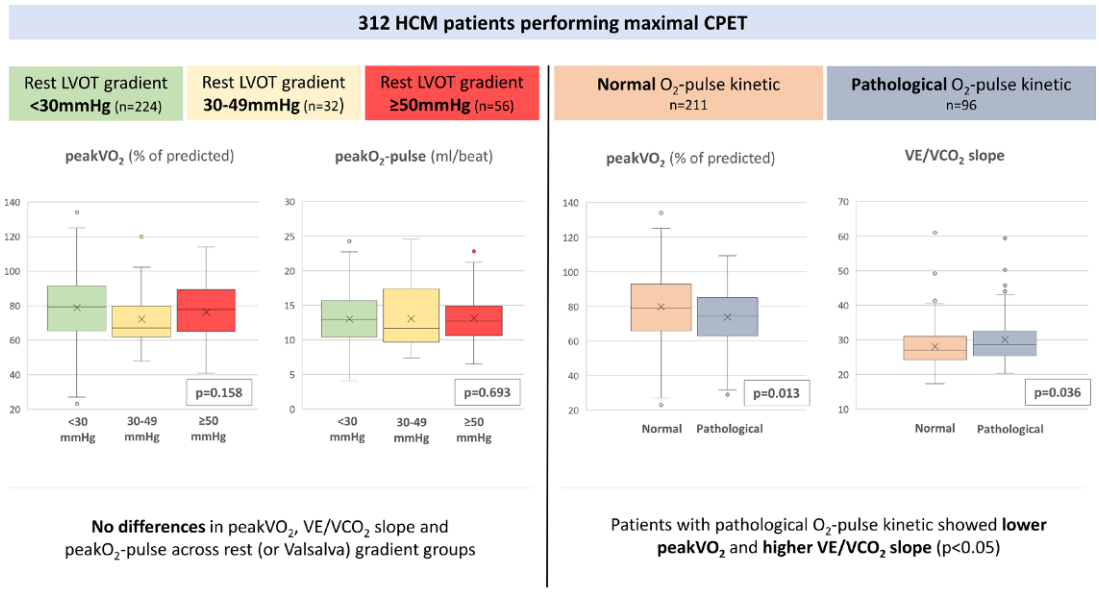

Figure 2 Main findings of the study. Dividing our HCM population according to baseline LVOT gradient, we did not observe significant differences in peak VO_2, VE/VCO_2 slope and peak O_2-pulse (left side). If the same population is split according to the O_2-pulse behaviour, patients with pathological O_2-pulse kinetic showed lower peak VO_2 and higher VE/VCO_2 slope (right side). CPET, cardiopulmonary exercise testing; HCM, hypertrophic cardiomyopathy; LVOT, left ventricle outflow tract; peak VO_2, peak oxygen uptake; VE/VCO_2, ventilation to carbon dioxide production.

anaerobic threshold, and the O_2-pulse, respectively. Two other parameters, the VO_2/work and the O_2-pulse/work relationship, reflect the exercise induced changes of CO and SV, respectively.

VO_2 in HCM

The presence and degree of LVOT gradient did not influence exercise performance and, in particular, no significant differences were observed among HCM groups in VO_2, both at peak exercise and at anaerobic threshold, after age and gender adjustment. Therefore, the present data, argue against the common assumption that the presence of LVOT pressure gradient at rest is associated with a reduced forward CO and, consequently, exercise performance. It is recognised, however, that some patients may develop or increase an LVOT pressure gradient during exercise regardless of its absence at rest or during Valsalva manoeuvre. Indeed, resting and Valsalva values may be poor predictors of the pressure gradient elicited by exercise.

O_2-pulse in HCM

According to the Fick's law, the product of SV and arteriovenous oxygen content difference (CaO_2-CvO_2) can be measured during exercise by the O_2-pulse, which is calculated as the VO_2/heart rate ratio ($VO_2/HR=SV\times(CaO_2-CvO_2)$). Physiologically, SV increases with the initiation of upright exercise, but after that point, it normally remains nearly unchanged during a CPET, whereas the systemic extraction of delivered oxygen (CaO_2-CvO_2) progressively rises in a nearly linear fashion, regardless of the level of cardiovascular impairment. Hence, the normal linear O_2-pulse increase through the rest of the exercise is attributable solely to the growing difference in arterial-mixed venous oxygen content (CaO_2-CvO_2). As a consequence, a failure of the O_2-pulse to increase at higher heart rates indicates a decrease in the forward SV. At peak exercise, we observed O_2-pulse values in the normal range, regardless of LVOT gradient at rest or during Valsalva manoeuvre. Moreover, O_2-pulse kinetic was similar in all LVOT pressure gradient groups.

The O_2-pulse kinetics are described by four possible behaviours (figure 1). Among them, early flattening or down-sloping are considered abnormal and, in the absence of relevant haemoglobin desaturation, indicate a reduced SV. Physiologically, the increase in O_2-pulse during exercise consists of two phases, the first is at the beginning of effort, when O_2-pulse increase is predominantly related to SV rise and the second, with workload progression, mainly due to the arteriovenous O_2 content difference widening. In case of a reduced SV, as in heart failure, the arteriovenous oxygen content difference widens at the beginning of exercise and thus the O_2-pulse reaches its highest values at low exercise loads and remains stable thereafter.[18 19] Thus, an early flattening of the O_2-pulse curve reflects a reduced or inadequately increasing SV[18] (figure 1C). Furthermore, in case of a sudden reduction in SV occurring during exercise (eg, myocardial ischaemia or exertional MR), a real down-sloping of O_2-pulse curve can be observed (figure 1D). In the current study, the presence of resting or Valsalva LVOT gradient was not associated with an O_2-pulse behaviour suggestive of abnormal SV increase. Differently, an abnormal O_2-pulse kinetic identified patients with a poorer exercise performance and higher VE/VCO_2 slope. However, we do not know whether the abnormal O_2-pulse kinetic is independently associated with a worse prognosis, as also suggested by the slightly higher VE/VCO_2 slope. Indeed, in patients with HCM, VE/VCO_2 slope has a relevant prognostic role and its analysis is recommended to assess the risk of sudden death and the need of implantable cardioverter defibrillator.[7]

VO_2/Work slope in HCM

The VO_2/work slope assesses the O_2 delivery to working muscles. In normal subjects, VO_2/work is characterised by a linear relationship of approximatively 10 mL/min/W. As demonstrated by Koike *et al*, the first part of the VO_2/work relationship is CO independent, but the second part, with higher workload, is strictly CO dependent.[20] Indeed, the VO_2/work flattening is considered as a clear evidence of O_2 delivery reduction due to forward SV

decrease.[13] However, in our study, it was a very rare event (only 2 cases out of 312 patients), in contrast with the evidence of an abnormal O_2-pulse kinetic in 96 cases. These two findings are not in antithesis, because the lack of VO_2/work down-sloping, even in case of SV reduction, may be related to the presence of a compensatory heart rate increase, which likely counterbalance the SV reduction suggested by the O_2-pulse kinetic behaviour. Of note, a possible role of peripheral abnormalities responsible for altered O_2-pulse kinetics cannot be excluded. However, these are unlikely to have a major impact because they would be present throughout the entire effort and manifested by a reduction of the VO_2/work slope or of the O_2-pulse/work relationship and not by O_2-pulse changes limited to the last part of exercise.

It must be underlined that previous studies showed a controversial role of LVOT gradients in producing limiting symptoms,[21 22] with heterogeneous responses from individual patients.

Pathophysiological explanation

The absence of correlation between LVOT gradient and exercise performance in patients with HCM is counterintuitive and deserves a pathophysiological explanation or, at least, an attempt of a pathophysiological hypothesis. Hypertrophy of the interventricular septum results in an anatomic reduction of the LVOT and alters the direction of anterograde blood flow in systole, with the effect of 'catching' the redundant mitral leaflets and pushing them towards the outflow tract itself, generating a systolic anterior motion of the mitral leaflets, the so-called SAM. SAM itself contributes to the obstruction of the LVOT and the genesis of the typical intraventricular gradient. Importantly, SAM is also associated with loss of mitral leaflet coaptation and functional valve insufficiency, with regurgitation jets typically directed infero-laterally into the left atrium.[23 24] Because obstruction is a classically dynamic phenomenon, there are a number of conditions that can cause or exacerbate it, such the Valsalva manoeuvre, dehydration, squatting, meals, alcohol, vasodilator or positive inotropic drugs and, in particular, exercise.[10 25–28] Indeed, in our population, patients with more severe baseline LVOT gradient (table 1) showed higher rates of significant MR at rest, but not the presence of CPET parameters associated with low CO, such as low O_2-pulse, abnormal O_2-pulse kinetic during effort, low VO_2 or VO_2/work relationship. Differently, an abnormal behaviour of O_2-pulse kinetic during exercise is observed in a sizeable proportion of our population (about one-third), but not predictable by rest or Valsalva LVOT gradient. As a matter of fact, indirect signs of exercise-induced MR and a consequent pulmonary pressure increase are also represented by a small, but significant, increase in VE/VCO_2 slope in patients with abnormal O_2-pulse kinetic (table 3). In addition, patients with HCM often present more or less advanced degrees of diastolic dysfunction, and previous studies have demonstrated the association between the latter and reduced CO, particularly during exercise.[29] Therefore, this should be considered an alternative or, more likely, concomitant explanation of SV reduction during effort, as suggested by a pathological O_2-pulse kinetic. The exact contribution of each component (diastolic dysfunction and MR) in reducing CO and increasing VE/VCO_2 slope is unknown, also considering their complicated interplay, with diastolic dysfunction being per se a possible additive cause of worsening MR during exercise (figure 3). In summary, taking together our findings, we hypothesised that in patients with an abnormal O_2-pulse behaviour, the observed peak VO_2 reduction and the slight increase in VE/VCO_2 slope are related to the onset of a dynamic MR, due to SAM and/or a diastolic dysfunction during exercise, leading to a significant decrease in SV not predictable by resting or Valsalva LVOT pressure gradient.

Clinical implications

Our study indicates that O_2-pulse kinetic may represent a new, effective and useful parameter in the functional assessment of patients with HCM, regardless of the degree of baseline LVOT obstruction. Despite the absence of current prognostic evaluation, this study may serve as a hypothesis generator for future research directed to evaluate the additional/complementary value of O_2-pulse kinetics in the titration of medical therapy and/or in the indication for surgical treatment. Regardless, a cardiometabolic evaluation with CPET may serve to identify those patients with indirect signs of reduced SV during exercise

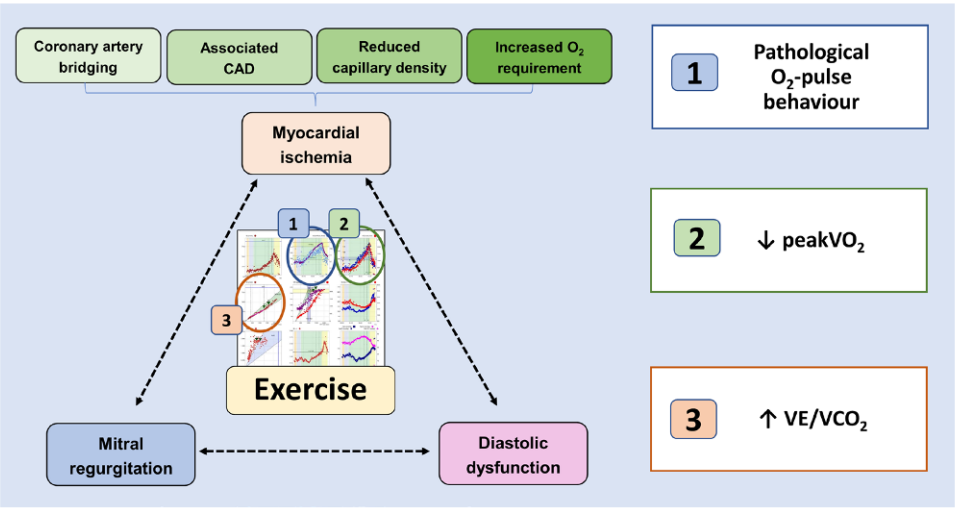

Figure 3 Pathophysiological explanation of exercise-induced changes observed in patients with HCM. Exercise-induced changes in HCM are driven by the complex interplay between myocardial ischaemia, diastolic dysfunction and mitral regurgitation (left side). More compromised patients showed a pathological O_2-pulse behaviour, reduced peak VO_2 and increased VE/VCO_2 slope at CPET (right side). CAD, coronary artery disease; CPET, cardiopulmonary exercise testing; HCM, hypertrophic cardiomyopathy; peak VO_2, peak oxygen uptake; VE/VCO_2, ventilation to carbon dioxide production.

to be candidates for further evaluation such as stress echocardiography or direct SV determination during exercise.

Study limitations

Our study has some limitations that are worthy of discussion. Despite being statistically robust and supported by exercise metabolic data collected in a sizeable HCM population, in absence of direct CO measurements or concomitant exercise echocardiography recording for MR and LVOT gradient assessment, our pathophysiological explanation is nothing more than a hypothesis. Also, the evaluation of the proportion of the exercise-induced MR compared with rest may be worth of interest. Similarly, a full assessment of the potentially relevant diastolic dysfunction—both at rest and during exercise—is missing.

Moreover, the definition of O_2-pulse early flattening adopted is based on a totally arbitrary cut-off and its interpretation is subject to some interoperator variability. On this regard, we must recognise that a formal inter-reader reproducibility assessment of O_2 pulse temporal behaviour analysis was not done. However, CPETs were interpreted by expert physicians daily involved in cardiopulmonary exercise evaluation.

Due to the retrospective design of the study, a potential selection bias (ie, patients with HCM not referred for CPET could have more favourable parameters) cannot be totally excluded. However, the data are collected in high-volume CPET centres, which routinely perform tests in the whole spectrum of HCM, both for clinical and research purposes.

Regardless of these limitations, the prognostic value of O_2-pulse kinetics during exercise seems to us an interesting concept which deserves future research and, indeed, further studies evaluating the prognostic impact of this variable on patients with HCM are warranted. Finally, no reproducibility data are available.

Conclusions

The interpretation of CPET in patients with HCM should be focused on O_2-pulse behaviour in addition to absolute value of O_2-pulse and other parameters influenced by CO such as VO_2 (both at anaerobic threshold and peak exercise), and the VO_2/work relationship, regardless of resting or Valsalva LVOT gradient. Adding the evaluation of O_2-pulse kinetics on top of the standard CPET, echocardiography and clinical parameters could lead to a potential incremental benefit in terms of HCM prognosis and therapeutic management. These aspects are particularly relevant given the absence of association between baseline LVOT gradient and functional limitation, as clearly demonstrated in our study.

Contributors Planning of the study: MMap, SRom, PA, DM, GS. Collection of data: MMap, SRom, MMer, MC, MMas, MMur, GG, MS, CC, DZ. Analysis: MMap, SRom. Paper drafting: MMap, SRom, DZ, PA, GS. Revisions: ES, IM, CV, FDM, SRov, CA. Overall guarantor: PA.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval This study involves human participants and was approved by Centro Cardiologico Monzino-IEO Ethic Committee (ID: R1540/21-CCM 1629). The study complies with the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The raw data of this study will be made public on www.zenodo.org and available for consultation after appropriate request.

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Key messages

What is already known on this subject?

⇒ Fatigue and dyspnoea leading to a reduced exercise performance are common symptoms in patients affected by hypertrophic cardiomyopathy (HCM).

⇒ Regardless of the underlying mechanism, a reduced forward cardiac output (CO) has been considered crucial for these symptoms' genesis.

What might this study add?

⇒ We evaluated the cardiopulmonary exercise testing (CPET) response in HCM focusing on parameters strongly associated with stroke volume and CO, such as oxygen uptake (VO_2) and O_2-pulse.

⇒ An abnormal O_2-pulse exercise behaviour correlates with reduced functional capacity helping identifying more advanced disease irrespectively of left ventricle outflow tract obstruction.

How might this impact on clinical practice?

⇒ Adding O_2-pulse kinetics evaluation to standard CPET could lead to a potential incremental benefit in terms of HCM prognostic stratification and, then, therapeutic management; however, further studies are needed to confirm this hypothesis.

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