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FULL RESEARCH PAPER
Exercise physiology & testing

Cardiopulmonary exercise testing parameters in healthy athletes vs. equally fit individuals with hypertrophic cardiomyopathy

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Aims Cardiopulmonary exercise testing (CPET) is often used when athletes present with suspected hypertrophic cardiomyopathy (HCM). While low peak oxygen consumption ($pV\dot{O}_2$) augments concern for HCM, athletes with HCM frequently display supranormal $pV\dot{O}_2$, which limits this parameter's diagnostic utility. We aimed to compare other CPET parameters in healthy athletes and equally fit individuals with HCM.

Methods and results Using cycle ergometer CPETs from a single centre, we compared ventilatory efficiency and recovery kinetics between individuals with HCM [percent predicted $pV\dot{O}_2$($ppV\dot{O}_2$) > 80%, non-obstructive, no nodal agents] and healthy athletes, matched (2:1 ratio) for age, sex, height, weight and $ppV\dot{O}_2$. Consistent with matching, HCM ($n = 30$, 43.6 ± 14.2 years) and athlete ($n = 60$, 43.8 ± 14.9 years) groups had similar, supranormal $pV\dot{O}_2$ (39.5 ± 9.1 vs. 41.1 ± 9.1 mL/kg/min, 125 ± 26 vs. 124 ± 25% predicted). Recovery kinetics were also similar. However, HCM participants had worse ventilatory efficiency, including higher early $V\dot{E}/V\dot{C}O_2$ slope (25.4 ± 4.7 vs. 23.4 ± 3.1, $P = 0.02$), higher $V\dot{E}/V\dot{C}O_2$ nadir (27.3 ± 4.0 vs. 25.2 ± 2.6, $P = 0.004$) and lower end-tidal CO_2 at the ventilatory threshold (42.9 ± 6.4 vs. 45.7 ± 4.8 mmHg, $P = 0.02$). HCM participants were more likely to have abnormally high $V\dot{E}/V\dot{C}O_2$ nadir (>30) than athletes (20 vs. 3%, $P = 0.02$).

Conclusion Even in the setting of similar and supranormal $pV\dot{O}_2$, ventilatory efficiency is worse in HCM participants vs. healthy athletes. Our results demonstrate the utility of CPET beyond $pV\dot{O}_2$ assessment in 'grey zone' athlete cases in which the diagnosis of HCM is being debated.

Lay summary We sought to examine exercise test findings in healthy athletes and equally fit individuals with a form of heart enlargement that commonly gets confused with 'athlete's heart' called hypertrophic cardiomyopathy (HCM) to see if elements of the exercise test could distinguish between these two groups. This is relevant as fit individuals often present for exercise testing as part of the work up to see if they have HCM or not, and getting the answer right is important because HCM is amongst the most common causes of sudden cardiac death in athletes.

- By design, individuals with HCM in this study were equally fit as the athletes, with both groups having fitness levels ('VO_2 max' levels) around 25% higher than expected for individuals of similar age and sex.
- Despite this similar and supranormal fitness, individuals with HCM had worse ventilatory efficiency than athletes. This is a metric that reflects how well the heart and lungs work together to get rid of the waste gas carbon dioxide during exercise. This finding should focus more attention on this parameter when exercise tests are being performed to evaluate for HCM in clinical practice.

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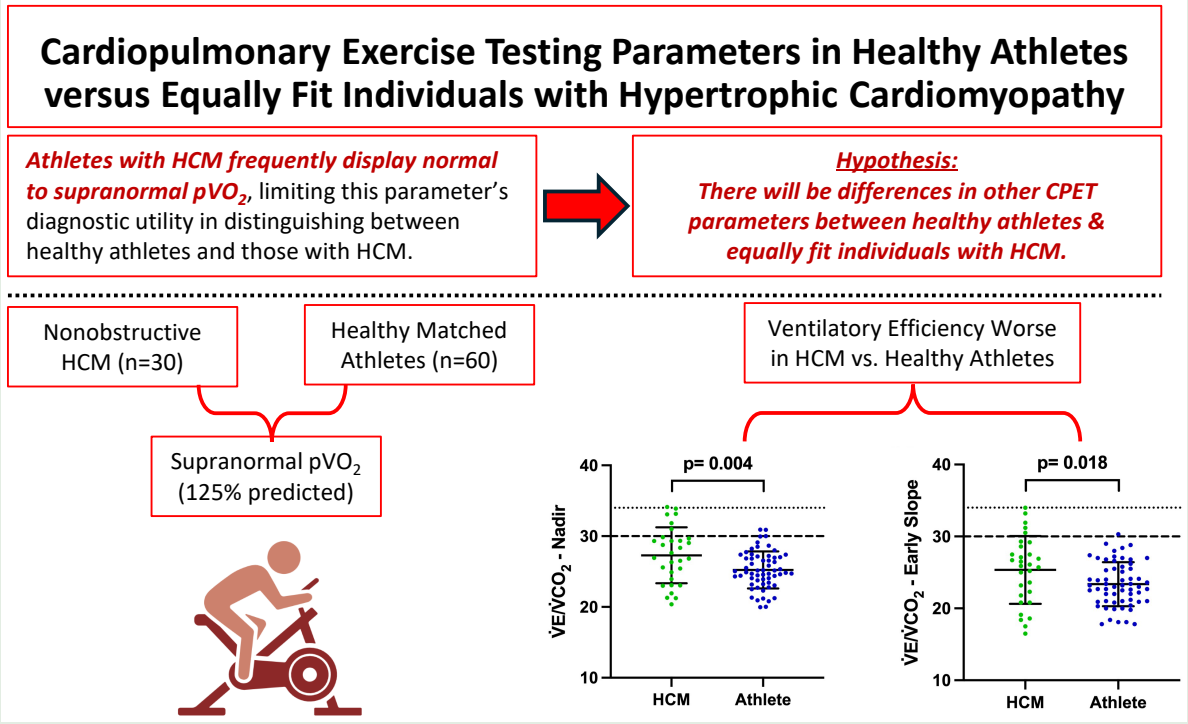
Graphical Abstract



Keywords Cardiopulmonary exercise testing • Hypertrophic cardiomyopathy • Athlete's heart

Introduction

Vigorous exercise training can result in cardiac enlargement that may overlap with mild forms of pathology, including hypertrophic cardiomyopathy (HCM). As HCM is amongst the common causes of sudden cardiac death in competitive sport, differentiating 'athlete's heart' from HCM has critical diagnostic implications.[1,2] While overt forms of HCM are obvious on cardiac imaging, mild left ventricular hypertrophy (LVH) may exist in both healthy athletes and individuals with phenotypically mild or evolving HCM. Metrics used to clarify the aetiology of this 'grey zone' LVH are derived from the general population and perform sub-optimally in athlete patients.[3] For example, athletes with HCM have larger left ventricular (LV) cavities and superior diastolic function when compared with sedentary HCM patients. Subsequently, these parameters when 'normal' in an undifferentiated athlete do not adequately reassure against HCM.[3] Overall, an optimal assessment of grey zone cases integrates the entirety of the patient's history, electrocardiogram, imaging and additional cardiac testing.[4]

Cardiopulmonary exercise testing (CPET) provides an objective assessment of functional capacity and is often used when athletes present for clinical evaluation of suspected pathology, including HCM.[5,6] Studies in the general population have demonstrated that individuals with HCM have cardiorespiratory fitness [peak oxygen consumption ($p\dot{V}O_2$)] that is lower than that of healthy controls.[5,7–9] Accordingly, it has been proposed that $p\dot{V}O_2$ <120% predicted may help differentiate HCM from benign physiologic LVH.[9] However, a sizable proportion of athletes with HCM display supranormal $p\dot{V}O_2$.[3] Therefore, in parallel with imaging metrics noted above, cardiorespiratory fitness, when normal, is not reassuring in cases of grey zone LVH.

Beyond peak parameters, CPET demonstrates many other aspects of exercise physiology that may differ in athletes with HCM, even in those with supranormal $p\dot{V}O_2$. One such parameter is ventilatory efficiency ($\dot{V}E/\dot{V}CO_2$), which reflects matching of alveolar ventilation and pulmonary perfusion as well as ventilatory drive.[10] Abnormally high $\dot{V}E/\dot{V}CO_2$ complements and may rival impaired $p\dot{V}O_2$ with regards to prognostic importance in the setting of cardiopulmonary disease.[11–13] No prior study has comprehensively examined CPET parameters in a physically fit population with HCM. Therefore, we sought to compare CPET parameters in healthy athletes and equally fit individuals with established HCM. In the setting of matched $p\dot{V}O_2$, we hypothesized that other CPET parameters, specifically ventilatory efficiency and recovery kinetics, would differ between healthy athletes and equally fit individuals with established HCM.

Methods

Study population and matching

This prospective cohort study included two groups, consisting of physically fit individuals with established HCM who were matched to healthy athletes as described below. Both groups underwent an intensity-graded, maximal effort-limited upright cycle ergometer CPET (Sport Excalibur Bicycle Ergometer, Lode, Holland) with continuous gas exchange monitoring (Ultima CardiaO2; Medgraphics Diagnostics, St Paul, MN, USA) for research or clinical evaluation in a single exercise laboratory from 1 October 2011 to 1 September 2022. Participant data including the results of CPET were prospectively collected and managed in a research database. The details of this database and the CPET protocol are previously described.[14] All study procedures were approved by the Mass General

Brigham Institutional Review Board. Tests performed for research and clinical indications utilized an identical protocol. Our basic inclusion criteria (cycle ergometer test, individuals ≥18 years of age, normal to supranormal exercise capacity (percent predicted $p\dot{V}O_2$ ($pp\dot{V}O_2$) > 80% using the Jones equation[15] on a maximal effort CPET [defined as respiratory exchange ratio (RER) > 1.05]) were met by 952 tests in the database.

From this subset of tests, as previously detailed, rigorous exclusion criteria using CPET results and medical chart review were used to generate a cohort of healthy athletes ≥18 years of age available for matching that was free from clinically evident cardiopulmonary disease.[14] Differing from this prior study,[14] the current study included all athletes, not just endurance athletes, included tests performed for research not just clinical tests, and extended the date of test inclusion from 1 October 2019 to 1 September 2022. In total, 228 tests on healthy athletes were deemed eligible for matching.

For the HCM cohort, from the 952 tests, 137 individuals were identified as possibly having HCM. This group was refined to include those who had non-obstructive HCM established on the basis of contemporary clinical guidelines,[16] were otherwise healthy (i.e. without other forms of cardiopulmonary disease that constituted exclusion criteria for the athlete cohort[14]), and had no prior septal reduction therapy and no utilization of nodal agents. In total, 53 tests on HCM participants were deemed eligible for matching. These individuals with HCM were matched as able to healthy athletes at a 1:2 ratio on the basis of $pp\dot{V}O_2$ (±10%), sex (exact), age (±5 years), weight (±5 kg) and height (±5 cm) to generate the final cohort in this study.

Cardiopulmonary exercise test parameters

All gas exchange data were analysed using a mid-5-of-7 averaging algorithm (i.e. the moving average of five breaths excluding the lowest and highest). $p\dot{V}O_2$ was defined as the highest oxygen uptake, averaged over 30 s, during the last minute of exercise. O_2 pulse curve shapes over test time were evaluated according to categories defined by Mapelli *et al.*[17] Specifically, normal O_2 pulse curve shapes were defined as those that either continuously upsloped or exhibited only late flattening (after at least two-thirds of loaded exercise had elapsed). Abnormal O_2 pulse curve shapes were defined as those that either exhibited early flattening (before two-thirds of loaded exercise had elapsed) or exhibited downsloping. End-tidal CO_2 ($PETCO_2$) was measured at rest and at the first ventilatory threshold (VT). Mixed expired CO_2 ($PECO_2$) was also measured at VT and the ratio of $PECO_2$ to $PETCO_2$ was assessed to evaluate relative contributions of pulmonary vs. cardiac disease.[18] $\dot{V}E/\dot{V}CO_2$-total slope was defined as the $\dot{V}E$ vs. $\dot{V}CO_2$ slope from the exercise ramp start to peak exercise, $\dot{V}E/\dot{V}CO_2$-early slope as the slope from the ramp start to VT, and $\dot{V}E/\dot{V}CO_2$-nadir as the lowest continuous 30 s average $\dot{V}E/\dot{V}CO_2$ ratio during exercise.[19] $\dot{V}E/\dot{V}O_2$ was calculated as a 10 s average at peak exercise and oxygen uptake efficiency slope (OUES) was defined as the slope of $\dot{V}O_2$ vs. the logarithmic equivalent of $\dot{V}E$.[20,21]

$\dot{V}O_2$ recovery kinetics were calculated using formulas previously described.[22] Briefly, $\dot{V}O_2$ recovery delay ($\dot{V}O_2RD$) was defined as the time from the end of loaded exercise until the $\dot{V}O_2$ permanently fell below $p\dot{V}O_2$. $\dot{V}O_2$ recovery half time ($T_{1/2}$) was defined as the time for $\dot{V}O_2$ to decrease to 50% of $p\dot{V}O_2$ adjusted for resting $\dot{V}O_2$. Heart rate recovery (HRR) was defined as change in heart rate (HR) from peak exercise to 2 min recovery. Measurement of HRR and $T_{1/2}$, which requires continuation of gas exchange and HR monitoring for a longer period of time post-exercise, were not possible in some participants owing to the nature of the CPET protocol utilized (i.e. some research tests were coupled with immediate post-exercise phlebotomy). When these were not available for individuals with HCM or athletes, their corresponding matches were also removed from the dataset for comparison of these metrics between groups.

Statistical analysis

Statistical analyses were performed using SPSS software (V.22; SPSS, IL, USA) and GraphPad Prism software, version 7.0 (GraphPad, Inc., San Diego, CA, USA). Before analyses, assumptions of normality were made using Shapiro–Wilk test (>0.05) and visualizations through histograms and Q-Q plots. Continuous variables are expressed as mean ± standard deviation (SD) or median and inter-quartile ranges (IQRs) as appropriate. Categorical variables are expressed as number of observations and frequencies (*n*, %).

To compare between the athlete and HCM groups, parametric testing (independent samples *t*-test) was used for normally distributed variables and non-parametric testing (Mann–Whitney *U* test) for variables that were not normally distributed. Differences between proportions were calculated by Fisher's exact test. In a subgroup analysis, the athlete and HCM groups were separately stratified by $pp\dot{V}O_2$ < 100 and ≥100 and by sex, and key analyses repeated by subgroup. Linear regression and Pearson correlation were used to assess the relationship between $PETCO_2$ at VT and $\dot{V}E/\dot{V}CO_2$ parameters, including $\dot{V}E/\dot{V}CO_2$-total slope, $\dot{V}E/\dot{V}CO_2$-early slope and $\dot{V}E/\dot{V}CO_2$-nadir. A value of $P < 0.05$ was considered significant for all analyses.

Results

Study population

Among 952 individuals referred for cycle ergometer CPET, 53 individuals with HCM and 228 healthy athletes were eligible for inclusion. Application of matching criteria yielded a cohort of 30 individuals with HCM who were able to be matched at a 1:2 ratio to 60 healthy athletes. Characteristics used for matching criteria are provided in *Table 1*. The mean age of this predominately male (80%, $n = 72$) and White (100%, $n = 90$) cohort was 43.7 ± 14.5 years. Participants had a mean weight of 80.0 ± 12.6 kg, height of 176.9 ± 8.3 cm and body mass index of 25.5 ± 3.3 kg/m^2. Consistent with matching, HCM and athletes had similar and supranormal $p\dot{V}O_2$ (39.5 ± 9.1 vs. 41.0 ± 9.0 mL/kg/min and 125 ± 27 vs. 124 ± 25%).

Additional characteristics of the HCM and athlete cohorts are shown in *Table 1*. The median maximal wall thickness (WT) in the HCM cohort was 16 mm (IQR 2 mm, Quartile 1–Quartile 3 bounds of 16–18 mm, 63% with WT ≤16 mm, $n = 2$ with WT 13–14 mm with family history of HCM). Most ($n = 17$, 56.7%) had apical predominant LVH, with the remaining having asymmetric septal predominant LVH ($n = 11$, 36.7%) and symmetric LVH ($n = 2$, 6.7%). Most of the HCM cohort were current competitive ($n = 9$, 30%) or recreational ($n = 10$, 33%) athletes.

Cardiopulmonary exercise testing parameters

Cardiopulmonary exercise testing characteristics are shown in *Table 2*. Baseline and peak exercise vital signs were similar with the exception of higher peak diastolic blood pressure (BP) in the HCM group [80 (13) vs. 78 (10) mmHg, $P = 0.002$]. In addition to the similar $p\dot{V}O_2$ conferred by matching, the two groups also had similar $\dot{V}O_2$ at VT (HCM: 28.7 ± 7.7 vs. athletes: 28.8 ± 8.1 mL/kg/min, $P = 0.982$). Assessment of recovery kinetics revealed similar HRR, $\dot{V}O_2RD$, and $T_{1/2}$ between groups (*Table 2*).

While most standard and novel CPET parameters did not differ between groups, individuals with HCM had worse ventilatory efficiency. Specifically, the HCM group had higher $\dot{V}E/\dot{V}CO_2$-early slope (25.4 ± 4.7 vs. 23.4 ± 3.1, $P = 0.018$) and $\dot{V}E/\dot{V}CO_2$-nadir (27.3 ± 4 vs. 25.2 ± 2.6, $P = 0.004$) compared with athletes (*Figure 1*). $\dot{V}E/\dot{V}CO_2$-total slope, which can be impacted by the degree of end exercise hyperventilation in highly fit individuals,[19] was similar in the two groups. Despite no difference in $PETCO_2$ at rest, the HCM group had lower $PETCO_2$ at VT (42.9 ± 6.4 vs. 45.7 ± 4.8, $P = 0.021$, *Figure 1*). $PETCO_2$ at VT was highly correlated with all $\dot{V}E/\dot{V}CO_2$ metrics, more so $\dot{V}E/\dot{V}CO_2$-nadir

Table 1 Cohort characteristics

	HCM ($n = 30$)	Athletes ($n = 60$)
Age, years	43.6 ± 14.2	43.8 ± 14.9
Sex, male	24 (80%)	48 (80%)
Race, White	30 (100%)	60 (100%)
Weight, kg	80.6 ± 14.9	79.7 ± 11.5
Height, cm	175.0 ± 7.1	177.8 ± 8.9
pp$\dot{V}O_2$, %	125 ± 27	124 ± 25
Current physical activity level[a]		
Competitive athlete	9 (30.0%)	28 (46.7%)
Competitive endurance athlete	7 (23.3%)	18 (30.0%)
Competitive Team athlete	2 (6.7%)	10 (16.7%)
Recreational athlete	10 (33.3%)	32 (53.3%)
Recreational endurance athlete	5 (16.7%)	14 (23.3%)
Recreational mixed sport athlete	5 (16.7%)	18 (30.0%)
Physically active	11 (36.7%)	0 (0%)
HCM morphology		
Apical predominant	17 (56.7)	
Asymmetric septal	11 (36.7)	
Symmetric	2 (6.7)	
HCM characteristics		
Maximal wall thickness, mm[b]	16 [2]	
ICD present at time of testing	1 (3.3%)	

Continuous variables are presented as mean ± SD or median [IQR]. Categorical variables are presented as *n* (%).
HCM, hypertrophic cardiomyopathy; pp$\dot{V}O_2$, per cent predicted peak oxygen consumption; CD, implantable cardioverter-defibrillator.
[a]Competitive athlete defined as one that regularly participates in organized competitions. Team athlete defined as one that competes as part of an organized team. Recreational athlete defined as one that regularly trains intensely with personal goals but does not compete against others. Endurance athlete defined as one that predominantly participates in endurance sports (i.e. running, cycling, rowing, swimming, and triathlon). Mixed sport athlete defined as one that participates in a mixture of sports, including endurance, team, lifting, and/or is regularly and intensely active as part of occupation (i.e. armed services or personal trainer). Physically active individuals defined as meeting at least guideline-recommended minimum recommended 'aerobic' activity levels (>150 min/week of moderate and/or >75 min/week of intense 'aerobic' physical activity).
[b]HCM participants had maximal WT of ≥15 mm with the exception of $n = 2$ individuals with 13–14 mm maximal WT in the setting of a documented family history of HCM. Maximal WT was derived from cardiac magnetic resonance imaging (CMR) in 25 participants and transthoracic echocardiography in 5 participants who did not have CMR data available (e.g. severe claustrophobia, low quality CMR, no recent CMR since ICD placement and outside CMR without available images).

Table 2 Cardiopulmonary exercise testing parameters

	HCM ($n = 30$)	Athletes ($n = 60$)
Effort and Vital Signs		
Peak RER	1.18 ± 0.1	1.20 ± 0.1
Baseline HR, b.p.m.	74 ± 15	70 ± 15
Peak HR, b.p.m.	166 ± 15	171 ± 14
Percent predicted	*94.6 ± 7.1*	*97.3 ± 6.9*
Baseline SBP, mmHg	125 ± 18	121 ± 13
Baseline DBP, mmHg	78 ± 8	78 ± 7
Peak SBP, mmHg	191 ± 35	184 ± 23
Peak DBP, mmHg	80 (13)	78 (10)*
Peak Work, W	291 ± 79	303 ± 70
Cardiovascular Performance		
p$\dot{V}O_2$, mL/kg/min	39.5 ± 9.1	41.1 ± 9.1
Percent predicted	*125 ± 26*	*124 ± 25*
$\dot{V}O_2$ at VT, mL/kg/min	28.7 ± 7.7	28.8 ± 8.1
Peak O_2 pulse, mL/beat	19.3 ± 4	19.1 ± 4.3
Abnormal O_2 pulse curve shape	5 (17%)	6 (10%)
Aerobic efficiency, mL/min/W	9.4 ± 1.0	9.7 ± 1.1
Ventilatory Efficiency		
$\dot{V}E/\dot{V}CO_2$-total slope	30.0 ± 5.5	28.2 ± 4.8
$\dot{V}E/\dot{V}CO_2$-early slope	25.4 ± 4.7	23.4 ± 3.1*
$\dot{V}E/\dot{V}CO_2$-nadir	27.3 ± 4.0	25.2 ± 2.6*
Baseline $PETCO_2$, mmHg	34.4 ± 4.4	35.6 ± 3.1
$PETCO_2$ at VT, mmHg	42.9 ± 6.4	45.7 ± 4.8*
$PECO_2$ at VT, mmHg	31.7 ± 4.9	33.5 ± 3.3*
$PECO_2/PETCO_2$ at VT	0.74 ± 0.03	0.73 ± 0.03
Peak exercise $\dot{V}E/\dot{V}O_2$	39.1 ± 6.5	37.3 ± 5.9
OUES	3.24 ± 0.72	3.36 ± 0.70
Recovery Kinetics		
HRR, b.p.m.[a]	43 ± 16	44 ± 15
$\dot{V}O_2$ recovery delay, s	1.0 (7.8)	2.5 (9.0)
$\dot{V}O_2$ recovery $T_{1/2}$, s[a]	59.5 ± 26.0	64.2 ± 18.6

Continuous variables are presented as mean ± SD or median (IQR).
b.p.m., beats per minute; DBP, diastolic blood pressure; HCM, hypertrophic cardiomyopathy; HR, heart rate; $PETCO_2$, partial pressure of end-tidal carbon dioxide; p$\dot{V}O_2$, peak oxygen consumption; SBP, systolic blood pressure, $\dot{V}E/\dot{V}CO_2$, ventilatory efficiency; VT, first ventilatory threshold.
[a]For HRR: HCM $N = 22$, matched athletes $N = 44$; for $\dot{V}O_2$ recovery $T_{1/2}$ HCM $n = 19$, matched athletes $N = 38$.
*$P < 0.05$ HCM vs. athletes.

($r = -0.92$, $P < 0.001$) and $\dot{V}E/\dot{V}CO_2$-early slope ($r = -0.88$, $P < 0.001$) than $\dot{V}E/\dot{V}CO_2$-total slope ($r = -0.77$, $P < 0.001$, *Figure 2*). When stratified by pp$\dot{V}O_2$, differences in ventilatory efficiency parameters between athlete and HCM groups remained directionally consistent within those with normal pp$\dot{V}O_2$ (80–100%, $n = 7$ HCM, $n = 14$ athletes) and supranormal pp$\dot{V}O_2$ (≥100%, $n = 23$ HCM, $n = 46$ athletes) as well as within males ($n = 24$ HCM, $n = 48$ athletes) and females ($n = 6$ HCM, $n = 12$ athletes, Supplementary material online, *Table*).

When analysis was focused only on the HCM participants with mildly increased WT (≤16 mm, range 13–16 mm), more akin to the range encountered in the evaluation of undifferentiated 'grey zone' LVH, $\dot{V}E/\dot{V}CO_2$-nadir remained significantly higher, i.e. worse when compared with their matched controls ($n = 19$ for HCM: 27.4 ± 4.3 vs. $n = 38$ for athletes 25.0 ± 2.6, $P = 0.01$, Supplementary material online, *Table*). Ventilatory efficiency was similar in the HCM subgroups with lesser WT (≤16 mm, $n = 19$) and greater WT (>16 mm, $n = 11$). Specifically $\dot{V}E/\dot{V}CO_2$-nadir in those with ≤16 mm WT was 27.4 ± 4.3 vs. 27.0 ± 3.4 in those with >16 mm WT ($P = 0.80$). $\dot{V}E/\dot{V}CO_2$-early slope in those with in ≤16 mm WT was 25.2 ± 5.4 vs. 25.5 ± 3.4 in those with in >16 mm WT ($P = 0.91$, Supplementary material online, *Table*).

A similar and sizable proportion of individuals with HCM and athletes had abnormally high $\dot{V}E/\dot{V}CO_2$-total slope when using the guideline-recommended cut-off of ≥30 (40.0 vs. 36.7%, $P = 0.82$) and the prognostically useful threshold of ≥34 (HCM: 23.3% vs. athletes:

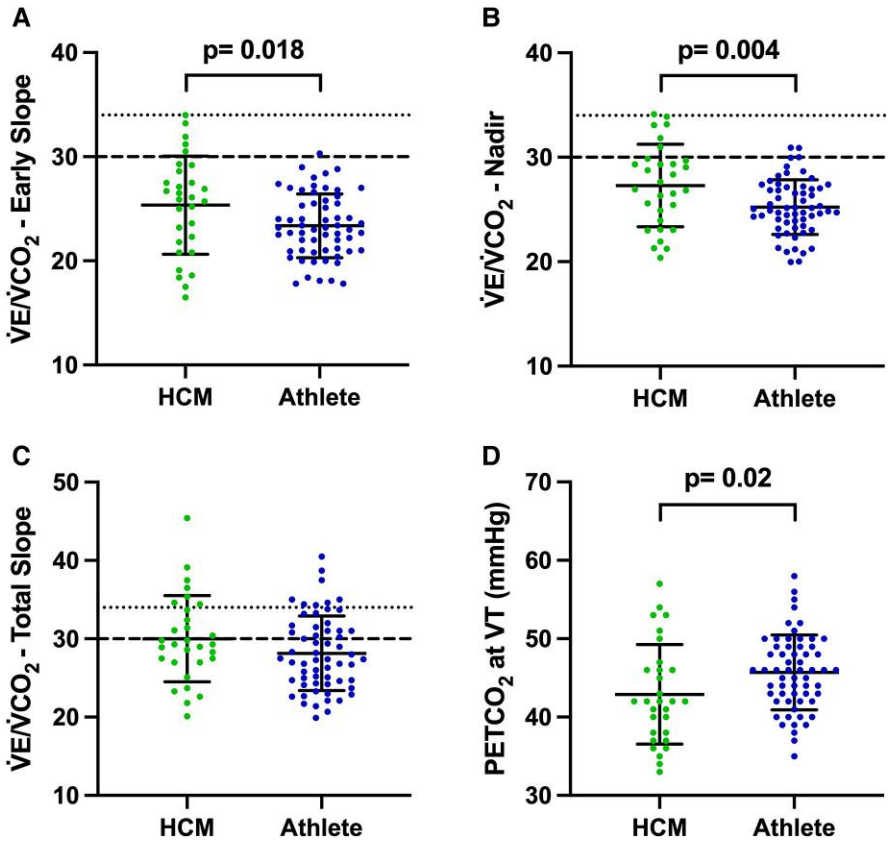


Figure 1 Ventilatory efficiency in healthy athletes vs. individuals with hypertrophic cardiomyopathy. Parameters of ventilatory efficiency measured as (*A*) $\dot{V}E/\dot{V}CO_2$-early slope (through *VT*), (*B*) $\dot{V}E/\dot{V}CO_2$-nadir, (*C*) $\dot{V}E/\dot{V}CO_2$-total slope and (*D*) $PETCO_2$ at ventilatory threshold in individuals with hypertrophic cardiomyopathy vs. athletes. Horizontal solid lines indicate mean and standard deviation. For (*A–C*), the interrupted and dotted lines indicate the guideline-recommended $\dot{V}E/\dot{V}CO_2$ cut-off of 30 and the prognostically useful threshold of 34, respectively.[10,13,23]

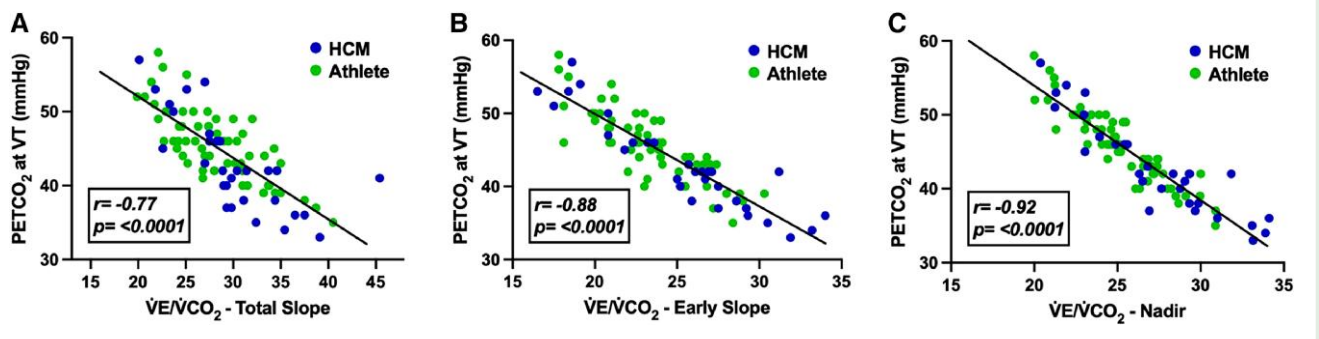


Figure 2 End-tidal CO_2 at the ventilatory threshold vs. $\dot{V}E/\dot{V}CO_2$ metrics. $PETCO_2$ correlation between $PETCO_2$ at ventilatory threshold and (*A*) $\dot{V}E/\dot{V}CO_2$-total slope (*B*) $\dot{V}E/\dot{V}CO_2$-early slope (through *VT*), (*C*) $\dot{V}E/\dot{V}CO_2$-nadir in individuals with hypertrophic cardiomyopathy vs. athletes. *R* value for Pearson correlation and corresponding *P*-value are shown.

13.3%, $P = 0.24$).[10,13,23] The use of $\dot{V}E/\dot{V}CO_2$-early slope and $\dot{V}E/\dot{V}CO_2$-nadir produced fewer abnormal values in both HCM and athlete groups. However, the HCM group had a significantly higher proportion of individuals with abnormal $\dot{V}E/\dot{V}CO_2$-early slope (≥30: HCM 16.7% vs. athletes: 1.7%, $P = 0.015$; sensitivity 17%, specificity 98%) and abnormal $\dot{V}E/\dot{V}CO_2$-nadir (≥30: 20 vs. 3%, $P = 0.015$, sensitivity 20%, specificity 97%). No athletes and only one (3.9%) individual with HCM had $\dot{V}E/\dot{V}CO_2$-nadir ≥34.

Discussion

With the goal of clarifying the utility of CPET parameters beyond $p\dot{V}O_2$ in grey zone cases of LVH, this study compared the CPETs of healthy athletes free of clinically evident cardiovascular disease and equally fit individuals with non-obstructive HCM. Between these two well-matched groups with similar and supranormal $p\dot{V}O_2$, submaximal CPET parameters (i.e. $\dot{V}O_2$ at VT), recovery kinetics and other parameters reflecting cardiovascular performance (i.e. peak O_2 pulse, aerobic efficiency) were similar. However, despite supranormal $p\dot{V}O_2$ in this fit HCM cohort, ventilatory efficiency was impaired relative to the athlete group, as reflected by higher $\dot{V}E/\dot{V}CO_2$-early slope, higher $\dot{V}E/\dot{V}CO_2$-nadir, and lower $PETCO_2$ at VT. While there was substantial overlap in the range of $\dot{V}E/\dot{V}CO_2$ values in the two groups, values exceeding the guideline-recommended cut-off were relatively common in fit individuals with established HCM and rare in athletes. Overall, our findings suggest that in grey zone clinical cases in which the diagnosis of pathologic vs. physiologic LVH is unclear in athletes, abnormal ventilatory efficiency should augment concern for HCM and merits inclusion alongside other diagnostic testing in the integrated assessment of such patients.

Vigorous exercise training provokes a range of well-described physiologic adaptations that manifest in athletes' diagnostic testing.[4] Prior work describing these adaptations has been centred on delineating what is normal for a healthy athlete, so as to better differentiate these physiologic changes from early pathology. However, the diagnostic utility of a given imaging or CPET parameter in this clinical grey zone has typically been assessed by comparing healthy athletes and patients with the relevant condition pulled from the general population.[9,24,25] This design does not replicate the relevant scenario encountered in clinical practice, in which an athlete, with exposure to exercise training far exceeding that represented in the general population, presents undifferentiated. Unsurprisingly, even when such athletes have HCM, they demonstrate imaging parameters and cardiorespiratory fitness that are superior to sedentary patients with HCM and therefore overlap more with those observed in the healthy athlete population.[3] This may be due to the overlay of exercise-induced adaptations onto their pathologic cardiac findings or due to selection, as athletes with milder HCM phenotypes and symptoms may be more likely to continue in sport. In this work, we were motivated to target the appropriate comparison of CPET parameters between fit individuals with established HCM and healthy athletes.

Our results are congruent with what others have demonstrated regarding imaging findings in athletes with HCM. Specifically, conventional echocardiographic parameters such as LV cavity size and diastolic function overlap substantially between healthy athletes and athletes with HCM.[3] Larger LV cavities and preserved diastolic function in athletes with HCM help explain our observation that several CPET parameters reflecting cardiovascular performance (i.e. $\dot{V}O_2$ at VT, aerobic efficiency, peak O_2 pulse and O_2 pulse curve shape) were similar between groups. In contrast to less fit HCM cohorts,[17] this suggests an intact ability to augment cardiac output (CO) or alternately enhanced peripheral adaptations facilitating oxygen extraction in fit individuals with HCM. We also evaluated recovery kinetics, which when prolonged have been demonstrated to reflect inadequate augmentation in exercise CO in other forms of cardiomyopathy.[22] The persistence of high HR and $\dot{V}O_2$ longer into recovery 'repays' accrued oxygen deficit conferred by inadequate CO during exercise. We hypothesized that these recovery kinetic parameters may reveal subtler differences between fit individuals with HCM and athletes that were not evident utilizing the traditional CPET parameters above. However, consistent with an intact CO response to exercise in these fit individuals with HCM, recovery kinetics also did not differ between groups.

In contrast, despite supranormal cardiorespiratory fitness, the HCM group demonstrated impaired ventilatory efficiency when compared with healthy athletes as assessed by several complementary CPET parameters. Ventilatory efficiency is important diagnostically and prognostically in the setting of cardiopulmonary disease,[10] particularly heart failure in which it complements and may even rival the prognostic importance of $p\dot{V}O_2$.[12,13] Impaired (i.e. high) $\dot{V}E/\dot{V}CO_2$ results either from reduced pulmonary perfusion relative to ventilation or from abnormally high ventilatory drive (high $\dot{V}E$), both of which can be sequalae of cardiomyopathy. In similar athletic HCM cohorts, resting diastolic function substantially overlaps with but is worse on average than that of healthy athletes.[3] While other CPET parameters in this study's HCM cohort suggest an intact CO response to exercise, we hypothesize that relative impairment in diastolic function conferred by their disease may result in higher LV and pulmonary filling pressures to achieve such COs, as reflected by the higher $\dot{V}E/\dot{V}CO_2$ observed. Since most fit individuals with HCM in this study have preserved $\dot{V}E/\dot{V}CO_2$, it is critically important to not be falsely reassured by this metric when normal. However, as is also true for abnormal diastolic function,[3] overtly abnormal $\dot{V}E/\dot{V}CO_2$ above cut-off values is very specific for HCM in this fit cohort. This finding supports integration of ventilatory efficiency in with other elements of the diagnostic evaluation in grey zone cases.

Importantly, we found the most substantial differences in ventilatory efficiency between groups utilizing either $\dot{V}E/\dot{V}CO_2$-early slope, which excludes data from after VT, or $\dot{V}E/\dot{V}CO_2$-nadir, which usually occurs around VT. $\dot{V}E/\dot{V}CO_2$-total slope was not different between groups. This highlights the relevance of choosing the appropriate method of evaluating ventilatory efficiency according to the population being studied. As we have previously demonstrated, athletes have the ability to sustain a graded exercise effort well beyond the respiratory compensation point, which occurs after the VT and is defined by a physiologic late-exercise increase in $\dot{V}E$ relative to $\dot{V}CO_2$.[19] This physiologic increase in late-exercise $\dot{V}E/\dot{V}CO_2$ slope, which is facilitated by supranormal cardiorespiratory fitness and intact pulmonary function, can 'pull up' the $\dot{V}E/\dot{V}CO_2$ slope when measured through end exercise ($\dot{V}E/\dot{V}CO_2$-total slope). This results in large proportion of misclassified 'abnormally high' $\dot{V}E/\dot{V}CO_2$-total slope values that do not reflect cardiopulmonary disease in athletic populations. As in our prior work,[19] we observed a high prevalence of abnormal $\dot{V}E/\dot{V}CO_2$-total slope in both the fit individuals with HCM and the athletes in this study. The prevalence of abnormal $\dot{V}E/\dot{V}CO_2$ decreased and between group differences were made evident by evaluation of ventilatory efficiency using $\dot{V}E/\dot{V}CO_2$-early slope and $\dot{V}E/\dot{V}CO_2$-nadir, underscoring that these parameters are better at identifying pathology in athletic, fit populations.

There are several limitations of this study. First, consistent with the population referred to this single centre, individuals were predominantly white and male. Future research is needed to assess for differences in more ethnically and sex-diverse populations. As $\dot{V}E/\dot{V}CO_2$ differs slightly on the basis of sex,[26] the stratified analysis reassures that our key results are directionally consistent in males and females. Second, some CPET findings may vary on the basis of recent exercise volume. While these data were not uniformly available for this cohort, the salient result (i.e. $\dot{V}E/\dot{V}CO_2$) from this study would not be expected to differ. While $\dot{V}E/\dot{V}CO_2$ is a well-established prognostic indicator in heart failure, data are less robust in HCM[27] and prognosis was not addressed by this study. Future work should establish the prognostic value of $\dot{V}E/\dot{V}CO_2$ in HCM patients with and without intact cardiorespiratory fitness. Cardiopulmonary exercise testing in these participants did

not include arterial blood gases or transcutaneous assessment of $\dot{V}CO_2$ for assessment of $PaCO_2$. Therefore, we are unable to ascertain which of the two major determinants of ventilatory efficiency (i.e. dead space to tidal volume ratio or $PaCO_2$) is driving between group differences. Lab personnel changed and equipment was updated over the span over which participants in this study were tested. Importantly, exercise protocols remained the same and tests for both groups were equally spread out over this period such that we do not anticipate that this impacted our results.

Finally, aligned with prior work in this space,[3] we compared healthy athletes to fit individuals with established HCM, who all lacked LV outflow tract obstruction and largely had mild phenotypes (63% with WT ≤16 mm). However, this study did not specifically study individuals with yet undifferentiated grey zone hypertrophy. Our design prioritized comparing groups whose members had a certain phenotype, but this leaves uncertainty about how CPET parameters would perform prospectively in a cohort of fit individuals with grey zone hypertrophy in which HCM has not been yet definitively ruled in or out. Ventilatory efficiency was still significantly worse in the HCM subgroup with the milder phenotypes when compared with matched athletes, and ventilatory efficiency was similar in HCM participants with only mildly increased WT vs. more overt LVH. This analysis supports the promising role of adding ventilatory efficiency to the list of parameters that are scrutinized in the comprehensive evaluation of grey zone cases.

Conclusions

The clinical evaluation of undifferentiated athletes with LVH in the grey zone is challenging, made more so by the fact that the imaging and CPETs of athletes with HCM will overlap more with those of healthy athletes than sedentary individuals with the same disease. In this assessment, CPET is commonly utilized to measure $p\dot{V}O_2$, which is helpful only when overtly abnormal as undifferentiated athletes will commonly present with preserved cardiorespiratory fitness. In this study, we demonstrate the utility of CPET beyond $p\dot{V}O_2$, revealing that impaired ventilatory efficiency is present in some fit individuals with HCM and highly specific to this population, being rare in equally fit athletes. As $\dot{V}E/\dot{V}CO_2$ overlaps substantially between groups, normal values should not falsely reassure. However, our results support inclusion of $\dot{V}E/\dot{V}CO_2$-early slope and $\dot{V}E/\dot{V}CO_2$-nadir in the integrated assessment of whether the athlete has pathologic or physiologic LVH and underscore the value of CPET beyond $p\dot{V}O_2$ assessment when performed in this setting.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Author contribution

C.M., S.K.G., B.J.P., A.F.T.-R., M.A.F., M.F.D. and M.M.W. have made contributions to the conception or design of the work. C.M., S.K.G., B.J.P., M.W.S., K.S.B., J.B.K., C.V. and M.M.W. contributed to the acquisition, analysis or interpretation of data for the work. C.M., K.S.B. and M.M.W. drafted the manuscript and figures, and all other authors (S.K.G., B.J.P., M.W.S., J.B.K., C.V., A.F.T.-R., M.A.F. and M.F.D.) critically revised the manuscript. All authors have given final approval of the manuscript, and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

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Data availability

Data available on request.

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