Integrating pulmonary function testing with cardiopulmonary exercise testing for enhanced stratification in hypertrophic cardiomyopathy

Robin Willixhofer ,[1,2] Massimo Mapelli,[1,2] Nikita Baracchini,[3,4] Nicola Campana,[1,5] Teresa Maria Capovilla,[3,4] Alessandro Nava,[6] Elisabetta Salvioni,[1] Carlo Vignati,[1] Jeness Campodonico,[1] Filippo Maria Rubbo,[1,3] Damiano Magrì,[7] Beatrice Pezzuto,[1] Irene Mattavelli,[1] Arianna Galotta,[1] Nicolò Capra,[1] Carriere Cosimo,[3] Irena Tavčar,[3] Maddalena Rossi,[3] Christian Cadeddu,[8] Marco Merlo,[3,4] Gianfranco Sinagra,[3,4] Piergiuseppe Agostoni[1,2]

For numbered affiliations see end of article.

Correspondence to
Dr Piergiuseppe Agostoni; piergiuseppe.agostoni@cardiologicomonzino.it

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ABSTRACT

Background Cardiopulmonary exercise testing (CPET) is essential for assessing patients with hypertrophic cardiomyopathy (HCM), but the role of pulmonary function testing (PFT) in refining patient stratification remains underexplored. This study investigates the relationship between PFT and CPET parameters in patients with HCM.

Methods In this prospective two-centre study, 102 clinically stable patients with HCM underwent PFT and CPET. Spearman's correlation and multiple linear regression were used to assess relationships between PFT (forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1)) and CPET variables, adjusting for confounders.

Results Patients exhibited preserved lung function (mean FVC: 90.7%; FEV_1: 92.5%). Strong correlations were observed between PFT and CPET metrics, including peak VO_2 (FVC: r=0.649, p<0.001; FEV_1: r=0.691, p<0.001) and peak ventilation (FVC: r=0.682, p<0.001; FEV_1: r=0.688, p<0.001). Regression analysis confirmed independent associations between PFT and CPET performance (all p<0.001).

Conclusion PFT metrics strongly correlate with CPET parameters in HCM, suggesting that PFT could complement CPET for a more comprehensive assessment of exercise capacity and patient stratification.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cardiopulmonary exercise testing (CPET) is a key tool for assessing exercise capacity and risk stratification in hypertrophic cardiomyopathy (HCM), but the role of pulmonary function testing (PFT) in this context is not well understood.

WHAT THIS STUDY ADDS

⇒ This study identifies strong, independent correlations between PFT metrics (forced vital capacity and forced expiratory volume in 1 s) and CPET parameters, suggesting PFT could enhance patient stratification and functional assessment in HCM.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Integrating PFT with CPET may improve sensitivity in detecting treatment effects in clinical trials and refine functional assessments in routine practice, particularly for patients with borderline CPET results or pulmonary impairment.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a complex phenotypic and genetic cardiac disorder characterised by left ventricular hypertrophy in the absence of abnormal loading conditions, which has been recently transformed to be pharmacologically treatable.[1 2] HCM manifests through a pathophysiological interplay including microvascular dysfunction, fibrosis, left ventricular outflow tract (LVOT) obstruction contributing to left ventricular diastolic dysfunction, arrhythmias and electrophysiological remodelling related to chronotropic incompetence. These mechanisms lead to exercise limitations, which can be objectively assessed by cardiopulmonary exercise testing (CPET), the gold-standard method to evaluate exertional dyspnoea.[3] CPET has emerged as a critical clinical trial tool in the assessment and evaluation of patients with HCM.[4–6] HCM poses challenges for prognostication due to its relatively low rates of early adverse events such as hospitalisation and mortality.[7] Instead, exercise-based metrics like peak oxygen consumption (VO_2) offer a meaningful alternative, correlating strongly with survival and progression to heart failure.[8] Clinical trials such as EXPLORER-HCM,[4] SEQUOIA-HCM[6] and ODYSSEY-HCM[9] used CPET to measure the treatment efficacy of mavacamten and aficamten by assessing CPET parameters, including VO_2 at peak exercise and ventilatory efficiency, depicted by the relationship between ventilation and carbon dioxide production (VE/VCO_2) slope.[5 10] Indeed, the VE/VCO_2 slope and the O_2 pulse, which represents oxygen consumption per heartbeat, have been shown to be independent predictors of outcomes, facilitating risk stratification and therapeutic decision-making in both asymptomatic and symptomatic patients.[3] Prior to each CPET, a pulmonary function test (PFT),

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Table 1 Baseline characteristics of the HCM cohort

Overall population (n=102)	
Variable	**Mean (SD) or median (IQR)**
Demographic and clinical data	
Male sex	80 (78.4%)
Age, years	53 (16)
Weight, kg	78.7 (14.2)
Height, cm	173 (9)
BMI, kg/m^2	25.8 (23.8–28.6)
Septal wall thickness, mm	18 (15–21)
LVOT gradient*	5.0 (0.0–42.8)
LVOTobstructionn	27 (26.5%)
SAM	41 (40.2%)
LVEF, %	62 (59–68)
Mitralinsufficiencyy (grade 2–3)	18 (17.6%)
Sinus rhythm	94 (93%)
AF or paced rhythm	7 (7%)
Pharmacological and procedural therapy	
β-Blockers	82 (80%)
Calcium antagonist	10 (10%)
Composite therapy†	86 (84%)
Disopyramide	3 (3%)
Previous myectomy	6 (6%)
Pulmonary function testing	
Forced vital capacity, L	3.9 (1.3)
Forced vital capacity, % predicted	90.7 (16.4)
FEV_1, L	3.2 (1.0)
FEV_1, % predicted	92.5 (17.0)
Cardiopulmonary exercise testing	
Peak VO_2, mL/min/kg	22.9 (7.8)
VO_2 at AT, mL/min/kg	12.9 (10.9–15.5)
VE/VCO_2 slope	29.5 (26.0–33.2)
Peak O_2 pulse, mL/beat	13.4 (3.7)
Peak O_2 pulse, % predicted	98.8 (83.2–113.8)
Peak VE, L/min	77 (26)
Breathing reserve, %	36.3 (28.0–42.0)
Peak RER	1.2 (0.1)
VO_2 work slope, mL/min/Watt	9.9 (8.8–10.5)
Peak, Watt	149.4 (60.6)
Peak $PetO_2$, mm Hg	119.8 (6.5)
Peak $PetCO_2$, mm Hg	33.4 (5.5)

Demographic, clinical, pulmonary function, cardiopulmonary exercise testing and non-invasive cardiac output measurements in the multicentric HCM population with values presented as mean±SD or median with IQR in brackets.
*36% of data were missing.
†Treated with at least one of both classes (β-blockers and/or calcium antagonists).
AT, anaerobic threshold; BMI, body mass index; FEV_1, forced expiratory volume in 1 s; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; $PetCO_2$, partial pressure of end-tidal carbon dioxide; $PetO_2$, partial pressure of end-tidal oxygen; RER, respiratory exchange ratio; SAM, systolic anterior motion; VE, minute ventilation; VE/VCO_2, ventilation to carbon dioxide production; VO_2, oxygen consumption.

including forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1), is conducted. The information yielded is primarily used to assess abnormalities in the pulmonary system. However, it has been shown that FEV_1 is linked to increased all-cause mortality rates within the general population,[11] suggesting that PFT could aid in refining HCM patient stratification. To test this hypothesis, we examined the correlation between key CPET variables associated with HCM outcomes and PFT measures. Regression analysis further assessed whether pulmonary function independently contributes to exercise capacity, providing deeper insight into the role of ventilatory function in patient stratification.

METHODS

This is a multicentric, prospective study that was conducted at two Italian referral centres (Cattinara Hospital, Trieste and Monzino IRCCS Cardiological Center, Milan) between January 2021 and March 2024.

Patient selection

We included patients with HCM who were clinically stable (≥6 months after hospitalisation, invasive procedures or changes in drug therapy), able to perform CPET and received guideline-directed medical therapy.

HCM was defined as a maximum left ventricular wall thickness ≥15 mm, or ≥13 mm in familial cases with positive genetic testing, or an abnormal ECG. Obstructive HCM was diagnosed when LVOT obstruction exceeded 30 mm Hg at rest or during stress.[12] Patients treated with myosin inhibitors (eg, mavacamten) were excluded to evaluate a solely disease-specific therapy-naïve cohort. Echocardiographic parameters were collected from the exam closest to CPET.

Study procedures

PFT included FVC and FEV_1. Tests were performed in a seated position with a nose clip and an antibacterial filter attached to the volume sensor for hygiene.

CPET was performed using a cycle-ergometer ramp protocol tailored to achieve peak exercise in 8–12 min. Testing was symptom-limited and analysed breath-by-breath. Key CPET parameters included peak VO_2 (highest VO_2 during the final 30 s of exercise). The anaerobic threshold (AT) was identified via the V-Slope analysis, ventilatory equivalents and end-tidal gas pressures. The VE/VCO_2 slope was calculated as the linear relationship between ventilation and CO_2 output during exercise. Reporting and evaluation of other CPET parameters were commenced as standard.[13]

The Vyntus CPX (Vyaire Medical) and Quark CPET (COSMED) metabolic carts were used, and data were re-analysed independently by three experienced operators.

Statistical analysis

Variables were reported as mean and SD if normally distributed, or median and IQR if skewed. Descriptive statistics included the mean (SD) or median (IQR) for continuous variables and counts (percentages) for categorical data. Correlation was assessed using Spearman's correlation coefficients to ensure robustness against non-linearity. Correlations were classified as strong ($r>0.6$), moderate ($0.4\leq r\leq 0.6$) or weak ($r<0.4$). False discovery rate correction using the Benjamini-Hochberg method addressed multiple comparisons. Multiple linear regression was used to evaluate associations between CPET and PFT variables while adjusting for potential confounders (body mass index (BMI), age, LVOT gradient, left ventricular ejection fraction). All analyses were performed in RStudio (V.2024.09.1+394) with R V.4.4.2. Statistical significance was set at $p<0.05$.

RESULTS

102 patients had a mean age of 53 years, were predominantly male (78.4%) and had a median BMI of 25.8 kg/m^2. Key clinical findings included LVOT obstruction in 26.5% of participants

Table 2 Relationships between selected CPET and PFT variables

Correlation						Linear regression adjusted for confounders (BMI, age, LVOT gradient and LVEF)			
CPET variable	PFT variable	Method	Coefficient	P value	FDR-adjusted p value*	Beta-coefficient	SE	Adjusted R^2	P value
Peak VO_2	FVC	Spearman	0.649	<0.001	<0.001	2.952	0.753	0.363	<0.001
	Per cent predicted FVC	Spearman	0.508	<0.001	<0.001	0.222	0.047	0.442	<0.001
	FEV_1	Spearman	0.691	<0.001	<0.001	5.825	1.021	0.484	<0.001
	Per cent predicted FEV_1	Spearman	0.498	<0.001	<0.001	0.233	0.045	0.472	<0.001
VE/VCO_2 slope	FVC	Spearman	−0.359	<0.001	<0.001	−1.230	0.730	0.170	0.097
	Per cent predicted FVC	Spearman	−0.304	0.002	0.003	−0.139	0.048	0.246	0.005
	FEV_1	Spearman	−0.356	<0.001	<0.001	−3.016	1.054	0.237	0.006
	Per cent predicted FEV_1	Spearman	−0.218	0.03	0.038	−0.134	0.047	0.241	0.007
Peak O_2 pulse	FVC	Spearman	0.591	<0.001	<0.001	1.431	0.360	0.260	<0.001
	Per cent predicted FVC	Spearman	0.262	0.009	0.011	0.054	0.026	0.160	0.041
	FEV_1	Spearman	0.574	<0.001	<0.001	2.947	0.473	0.436	<0.001
	Per cent predicted FEV_1	Spearman	0.298	0.003	0.004	0.061	0.025	0.181	0.017
Peak HR	FVC	Spearman	0.495	<0.001	<0.001	7.023	2.493	0.322	0.007
	Per cent predicted FVC	Spearman	0.394	<0.001	<0.001	0.620	0.165	0.382	<0.001
	FEV_1	Spearman	0.534	<0.001	<0.001	14.021	3.554	0.393	<0.001
	Per cent predicted FEV_1	Spearman	0.336	<0.001	<0.001	0.636	0.160	0.396	<0.001
Peak RER	FVC	Spearman	0.181	0.071	0.085	0.005	0.010	0.075	0.603
	Per cent predicted FVC	Spearman	0.157	0.119	0.138	0.000	0.001	0.068	0.763
	FEV_1	Spearman	0.198	0.047	0.058	0.011	0.015	0.080	0.453
	Per cent predicted FEV_1	Spearman	0.057	0.571	0.571	0.000	0.001	0.066	0.935
VO_2 at AT	FVC	Spearman	0.482	<0.001	<0.001	1.648	0.454	0.363	<0.001
	Per cent predicted FVC	Spearman	0.369	<0.001	<0.001	0.105	0.029	0.395	<0.001
	FEV_1	Spearman	0.530	<0.001	<0.001	3.014	0.657	0.429	<0.001
	Per cent predicted FEV_1	Spearman	0.368	<0.001	0.001	0.111	0.029	0.415	<0.001
Peak $PetCO_2$	FVC	Spearman	0.283	0.004	0.006	0.773	0.599	0.106	0.202
	Per cent predicted FVC	Spearman	0.128	0.204	0.223	0.070	0.041	0.124	0.091
	FEV_1	Spearman	0.319	0.001	0.002	2.005	0.876	0.157	0.026
	Per cent predicted FEV_1	Spearman	0.082	0.419	0.431	0.061	0.041	0.114	0.138
Peak VE	FVC	Spearman	0.682	<0.001	<0.001	10.296	2.296	0.339	<0.001
	Per cent predicted FVC	Spearman	0.418	<0.001	<0.001	0.549	0.163	0.276	0.001
	FEV_1	Spearman	0.688	<0.001	<0.001	19.797	3.056	0.484	<0.001
	Per cent predicted FEV_1	Spearman	0.437	<0.001	<0.001	0.580	0.158	0.299	<0.001

This table shows the correlations between CPET variables and PFT variables. Correlations were assessed using Pearson's or Spearman's correlation depending on data normality, with the correlation coefficient and p value reported for each variable pair. Positive and negative correlations highlight the relationship between exercise performance metrics and pulmonary function measures.

*Benjamini-Hochberg FDR correction.

AT, anaerobic threshold; BMI, body mass index; CPET, cardiopulmonary exercise testing; FDR, false discovery rate; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HR, heart rate; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; O_2 pulse, oxygen pulse; $PetCO_2$, partial pressure of end-tidal carbon dioxide; PFT, pulmonary function test; RER, respiratory exchange ratio; VE, minute ventilation; VE/VCO_2, ventilation to carbon dioxide production; VO_2, oxygen consumption.

and systolic anterior motion in 40.2%. Pulmonary function testing showed preserved lung function, with mean FVC and FEV_1 predicted values >90%. CPET revealed a mean peak VO_2 of 22.9 mL/min/kg and a median VE/VCO_2 slope of 29.5, indicating efficient ventilatory efficiency in most participants. Detailed demographic and clinical data are summarised in table 1.

Correlation between CPET and PFT variables

Peak VO_2 and VO_2 at the AT were both positively correlated with FVC and FEV_1. Peak VO_2 showed strong positive correlations with both FVC (r=0.649, p<0.001) and FEV_1 (r=0.691, p<0.001), as well as moderate correlations with their per cent predicted values. Similarly, VO_2 at AT demonstrated moderate positive correlations with FVC (r=0.482, p<0.001) and FEV_1 (r=0.530, p<0.001), suggesting that better exercise performance at the AT is also related to better pulmonary function.

The VE/VCO_2 slope and peak $PetCO_2$ both showed correlations with pulmonary function. The VE/VCO_2 slope showed weak negative correlations with FVC (r=−0.359, p<0.001) and FEV_1 (r=−0.356, p<0.001), indicating that a higher slope, reflecting inefficient ventilation, might be associated with lower pulmonary function in HCM. Peak $PetCO_2$ demonstrated weak positive correlations with FVC (r=0.283, p=0.004) and FEV_1 (r=0.319, p=0.001), emphasising the link between ventilatory efficiency and pulmonary function.

Peak minute ventilation (VE) showed strong positive correlations with FVC (r=0.682, p<0.001) and FEV_1 (r=0.688, p<0.001), indicating that higher peak ventilation during exercise is strongly associated with better pulmonary function.

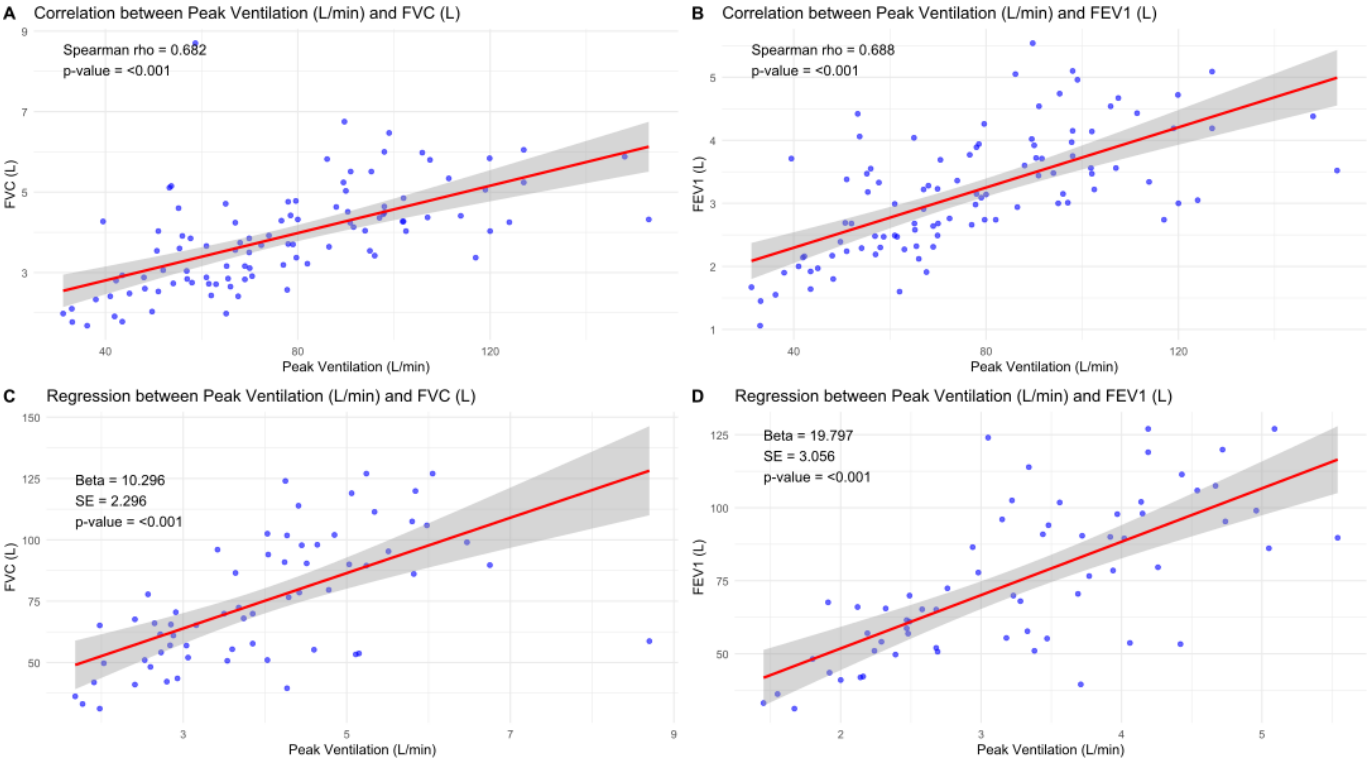

Figure 1 Relationships between PFT variables and peak ventilation during CPET scatter plots for FVC (A, C) and FEV_1 (B, D) in relation to peak ventilation measured during CPET. The depicted strong correlations (red line with significant correlation coefficients in the upper corners) highlight the link between PFT and CPET for evaluating patients with hypertrophic cardiomyopathy. Panels C and D additionally show regression analyses adjusted for BMI, age, LVOT gradient and LVEF, with beta-coefficients (β), SEs and p values displayed. BMI, body mass index; CPET, cardiopulmonary exercise testing; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; PFT, pulmonary function testing; p value, measure of statistical significance; Spearman's rho, correlation coefficient derived from Spearman's correlation.

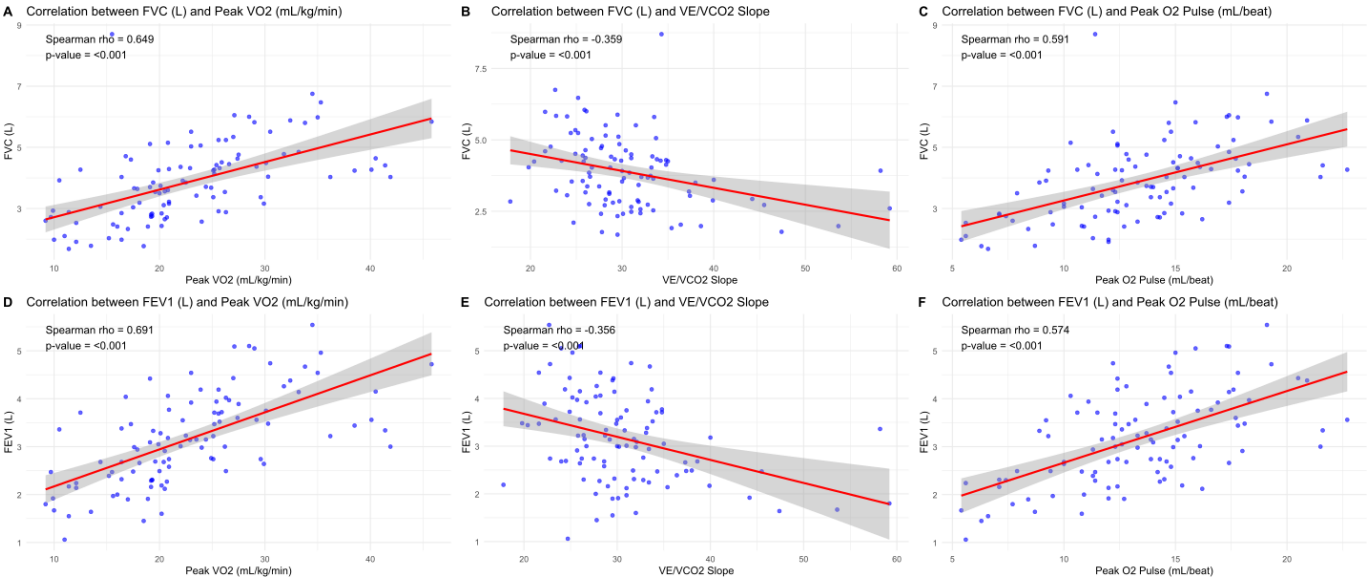

Figure 2 Correlation between key CPET variables and PFT measures. Scatter plots illustrate the relationships between FVC and FEV_1 with peak VO_2 (A, D), VE/VCO_2 slope (B, E) and peak O_2 pulse (C, F). Spearman's or Pearson's correlation coefficients and associated p values are shown for each panel. Panels A–C depict correlations with FVC, while panels D–F depict correlations with FEV_1. Strong associations were observed, particularly with peak VO_2 and peak O_2 pulse. CPET, cardiopulmonary exercise testing; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; O_2 pulse, oxygen pulse; p value, measure of statistical significance; Spearman's rho, correlation coefficient derived from Spearman's correlation; VE/VCO_2, relationship between ventilation and carbon dioxide production; VO_2, peak oxygen consumption.

Regression analysis showed that peak VO_2 (FVC: β=2.952, FEV_1: β=5.825), VO_2 at AT (FVC: β=1.648, FEV_1: β=3.014) and peak ventilation (VE) (FVC: β=10.296, FEV_1: β=19.797) were significantly associated with pulmonary function (all p<0.001). Full correlation and regression results, along with selected scatter plots, are presented in table 2 and figures 1 and 2. Full correlation and regression results, along with selected scatter plots can be seen in table 2, figures 1 and 2.

DISCUSSION

Our study is the first to highlight a robust relationship between pulmonary function metrics (both FVC and FEV_1) and CPET parameters in patients with HCM (table 2 and figures 1 and 2), even after adjusting for confounders. The strong correlation of peak VO_2 with PFT values underscores the importance of preserved pulmonary function in supporting oxygen delivery alongside oxygen pulse kinetics during exertion in HCM.[14] The weak negative correlation between the VE/VCO_2 slope and PFT variables might suggest that a lower pulmonary reserve contributes to inefficient ventilation and a higher ventilatory demand during exercise, which is further emphasised by the strong positive correlation of PFT with peak ventilation. In fact, a high VE/VCO_2 slope is linked to pulmonary congestion, which is commonly seen in patients with HCM.[15] Importantly, the positive correlation between peak $PetCO_2$ and pulmonary function metrics further suggests that better ventilatory efficiency supports improved gas exchange during exertion. Moreover, the regression analysis confirms that PFT independently contributes to CPET performance, suggesting that better pulmonary function supports better exercise capacity.

The demonstrated relationship between PFT metrics and CPET parameters reinforces the value of PFT in complementing CPET for a more comprehensive assessment of both pulmonary and cardiovascular function. While CPET has been widely used in clinical trials, adding PFT measures could refine end point definitions and capture therapeutic effects in clinical trials more comprehensively.[4 6]

In fact, a recent study normalised peak VO_2 and VE/VCO_2 slope values to a composite z-score to evaluate treatment efficacy.[5] Building on this method, integrating PFT parameters into such composite scores could further enhance their ability to assess functional improvements and therapeutic impact, particularly in patients with concomitant pulmonary disease. This approach is particularly relevant in trials of novel therapies, such as myosin inhibitors, which may influence both cardiovascular[4 6] and ventilatory performance.[16] As current HCM trials primarily rely on CPET-derived end points, incorporating PFT could enhance sensitivity in detecting treatment effects, particularly in patients with borderline CPET results or concomitant pulmonary impairment.

Conclusion

CPET parameters, particularly peak VO_2, VO_2 at AT and peak ventilation, correlate well with PFT in patients with HCM. Regression analysis confirms these associations, emphasising the role of PFT in providing a comprehensive physiological assessment. Furthermore, the integration of PFT alongside CPET into study designs for the assessment of treatment efficacy holds promise to enhance sensitivity and specificity of HCM-specific study outcomes.

Author affiliations
[1]Centro Cardiologico Monzino Istituto di Ricovero e Cura a Carattere Scientifico, Milan, Italy
[2]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy
[3]Center for Diagnosis and Treatment of Cardiomyopathies, Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Trieste, Italy
[4]Postgraduate School of Cardiovascular Medicine University of Trieste, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Trieste, Italy
[5]Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy
[6]Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Trieste, Italy
[7]Department of Clinical and Molecular Medicine, Azienda Ospedaliera Sant'Andrea, University of Rome La Sapienza, Rome, Italy
[8]Department of Medical Sciences and Public Health, Cardiology Unit, University Hospital Duilio Casula—Azienda Ospedaliero, University of Cagliari, Cagliari, Italy

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Contributors RW: conceptualisation, formal analysis, investigation, writing—original draft and revision. MMa, NCa, TMC, AN, CV, FMR, BP, IM, NCap, CCo, IT, MMe: data curation. MMa, ES, DM, PA: writing—review and editing. JC, AG: assisted with manuscript revision. NB, MR, CCa: investigation. GS: supervision (Trieste). PA: overall supervision, conceptualisation, writing—review and editing. All authors meet the authorship criteria of the International Committee of Medical Journal Editors (ICMJE). They made substantial contributions to the study, reviewed and approved the final manuscript and agreed to be accountable for the work. PA is the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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

Ethics approval This study was approved by Local Ethics Committee Centro Cardiologico Monzino (ID: R1638/22 CCM 1750). 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.

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ORCID iD
Robin Willixhofer http://orcid.org/0000-0003-3405-5715

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