Exercise-induced pulmonary hypertension in hypertrophic cardiomyopathy: a combined cardiopulmonary exercise test—echocardiographic study

Federica Re · Geza Halasz · Francesco Moroni · Matteo Beltrami · Pasquale Baratta · Andrea Avella · Elisabetta Zachara · Iacopo Olivotto

Abstract
Pulmonary arterial hypertension (PAH), documented in a significant portion of hypertrophic cardiomyopathy (HCM) patients, has been shown to adversely impact prognosis. In most HCM patients congestive symptoms are consistently elicited by exercise, thus suggesting the need for a provocative test to assess cardiac hemodynamics during effort. Combining cardiopulmonary exercise test (CPET) with echocardiography, we aimed to evaluate the presence of exercise induced pulmonary arterial hypertension (EiPAH), its role in functional limitation and its prognostic significance in a cohort of patients with obstructive and non-obstructive HCM. Study population included 182 HCM patients evaluated combining CPET and stress echocardiography. Left-ventricular outflow tract (LVOT) velocities, trans-tricuspid gradient, and cardiopulmonary variables were continuously measured. Thirty-seven patients (20%) developed EiPAH, defined as systolic pulmonary arterial pressure (sPAP) > 40 mmHg during exercise. EiPAH was associated with lower exercise performance, larger left atrial volumes, higher LVOT gradient and higher VE/VCO₂ slope. At multivariable analysis baseline sPAP (p < 0.0001) and baseline LVOT obstruction (p = 0.028) were significantly associated with EiPAH. Kaplan–Meier curve analysis showed EiPAH was a significant predictor of HCM-related morbidity (Hazard Ratio 6.21, 95% CI 1.47–26.19; p = 0.05; 4.21, 95% CI 1.94–9.12; p < 0.001 for the primary and the secondary endpoint respectively). EiPAH was present in about one fifth of HCM patients without evidence of elevated pulmonary pressures at rest and was associated with adverse clinical outcome. Diagnosing EiPAH by exercise echocardiography/CPET may help physicians to detect early stage of PAH thus allowing a closer clinical monitoring and individualized therapies.

Keywords Pulmonary arterial hypertension · Hypertrophic cardiomyopathy · Cardiopulmonary exercise test · Exercise induced pulmonary arterial hypertension

Introduction
Hypertrophic cardiomyopathy (HCM) is the most common inheritable cardiomyopathy, characterized by cardiac hypertrophy in the absence of an identifiable hemodynamic etiology [1]. Pulmonary arterial hypertension (PAH), can be found in about 11% of HCM subjects and has been shown to adversely impact prognosis [2, 3]. According to the classic paradigm, elevation of pulmonary pressures in HCM is attributable to chronic increase of left-sided diastolic pressures, which may be due to multiple concurrent causes, including diastolic dysfunction, left ventricular outflow tract (LVOT) obstruction, with or without secondary mitral regurgitation, as well as varying degrees of left ventricular systolic dysfunction [4, 5]. In a recently published cohort of
162 obstructive HCM subjects in whom systolic pulmonary artery pressures (sPAP) were measured invasively, however, 11% met the hemodynamic criteria for precapillary PAH, suggesting a concurring role of primary changes in pulmonary vascular resistance at least in a subset of patients [6]. In most HCM patients, despite normal pulmonary pressures at rest, congestive symptoms are consistently elicited by exercise, suggesting the need for provocative test to assess cardiac hemodynamics during effort. Exercise-induced PAH (EiPAH) is defined by a mean sPAP > 30 mmHg on exercise, measured invasively, in the presence of normal resting pulmonary hemodynamics [7, 8]. However, sPAP may now be reliably estimated non-invasively by echocardiography. Previous works on exercise echocardiography have validated a sPAP of 40 mmHg as a cut off for identifying EiPAH [9, 10]. Notably, EiPAH has been shown to precede the development of manifest disease in primary PAH and in PAH secondary to connective tissue disease [11]. It has also been established that abnormalities in pulmonary hemodynamics are a cardinal feature of exercise limitation in both Heart Failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) [12]. However, limited data are available regarding EiPAH and its role in determining functional impairment in HCM [13]. In the present study, combining cardiopulmonary exercise test (CPET) with echocardiography, we therefore aimed to evaluate the presence of EiPAH, its role in functional limitation and its prognostic significance in a cohort of patients with obstructive and non-obstructive HCM.

Materials and methods

Study design and population studied

Between March 2005 and November 2015, 235 patients with HCM referred to our tertiary referral center (Ospedale San Camillo-Forlanini, Rome, Italy) underwent combined CPET and stress echocardiography. Diagnosis of HCM was made according to current guidelines (1) based on the demonstration of a hypertrophied (wall thickness ≥ 15 mm), non-dilated left ventricle in the absence of other cardiac or systemic diseases capable of producing a similar degree of hypertrophy. Patients were excluded if presenting one of the following criteria: (1) permanent atrial fibrillation (AF), (2) inability to exercise due to advanced age or heart failure symptoms resulting from the “end-stage” phase of HCM with systolic dysfunction (LVEF < 50%), (3) prior history of septal myectomy or alcohol septal ablation, (4) prior documentation of ventricular tachyarrhythmia on effort or exertional syncope. In 26 cases sPAP could not be sampled during baseline echocardiographic evaluation, while in 14 additional patients sPAP could not be measured at peak exercise for technical reasons (poor acoustic window). Ten subjects presented baseline sPAP > 36 mmHg, therefore leading to the diagnosis of resting PAH. Therefore, 50 of the initial 235 subjects (21%) were excluded from the present analysis. Three additional patients did not have follow-up visits. Accordingly, the final study population included 182 HCM patients (35% females, mean age 47.5 ± 15.9). All subjects were in sinus rhythm at the time of enrollment.

The study conforms to the principles of the Helsinki declaration and the local institutional review boards approved the study protocol. Study participants gave informed consent to participate.

Exercise echocardiography and cardiopulmonary test

A comprehensive baseline echocardiogram was performed at rest with a Vivid 7 ultrasound system (GE Ultrasound, Norway). Diastolic function was assessed according to current guideline [14]. Symptom-limited CPET was then performed on a bicycle ergometer in the upright position, using a 10 Watt per minute ramp protocol. All patients maintained preexisting pharmacological treatment. Cardiopulmonary variables, oxygen uptake (VO₂ ml/min) and carbon dioxide production (CO₂ ml/min), were continuously measured with breath-by-breath analysis. Prior to each test, the equipment was calibrated using reference gases. Oxygen saturation monitoring was performed by pulse oximetry. Twelve-lead ECG, blood pressure and heart rate were recorded at rest and at each exercise step.

An abnormal blood pressure response was defined by either a failure of systolic blood pressure to rise > 20 mmHg or any fall in systolic blood pressure during exercise. Peak oxygen uptake (peak VO₂) was defined as the highest VO₂ level achieved during the final 30 s of the exercise test. The peak VO₂ was expressed as an absolute value per unit of body weight (ml/kg/min) and as percentage of predicted value. Anaerobic threshold (AT) was determined by the V-slope method and by analysis of ventilatory equivalents (VE). Ventilatory efficiency, obtained dividing VE by CO₂ production, reflects the relation between pulmonary ventilation and perfusion during exercise [15]. Exercise was considered adequate if the respiratory gas exchange ratio (RER) exceeded the value of 1.0. During CPET, LVOT velocities and trans-tricuspid gradient were measured during the last minute of each workload step. Non-invasive estimation of PAP was based upon a trans-tricuspid gradient calculated from the maximum velocity (V) of continuous Doppler tricuspid regurgitation taken from multiple views, using the modified Bernoulli formula. Estimated right atrial pressure (RAP) was determined from the size and collapsibility of the inferior vena cava. sPAP is the sum of right ventricular + right atrial pressure.
pressure [16]. All patients had continuous-wave Doppler assessment through the right ventricle outflow tract to exclude obstruction to flow. Immediately after each gradient was recorded, the degree of systolic anterior motion of the mitral valve (SAM) and mitral regurgitation were assessed in the apical and/or parasternal long-axis views. SAM was graded semi-quantitatively from 2-dimensional images or derived from M-mode recordings using a previously described grading system [17]. At the end of exercise, all patients continued recovery phase standing on the bicycle while LVOT velocities and diastolic function were recorded every minute for 5 min [18]. All data were digitally stored, and measurements were made at completion of each study.

**Study endpoints and patients follow-up**

The primary endpoint for this study was a composite of all-cause death, heart transplantation or aborted sudden cardiac death. Appropriate discharges from an implantable cardioverter defibrillator for ventricular fibrillation or sustained ventricular tachycardia were considered as sudden cardiac death equivalents. The secondary endpoint was defined as a composite of all-cause death, heart transplantation, aborted sudden cardiac death, nonfatal myocardial infarction, nonfatal stroke or hospitalization for decompensated HF. Follow-up was obtained by clinical visits and/or through telephone contacts. Referring cardiologists, general practitioners, and patients were contacted whenever necessary for further information.

**Statistical analysis**

All continuous variables were tested for normality using Shapiro–Wilk normality test and are expressed as mean ± standard deviation (SD) or median [interquartile range (Q1–Q3)] as appropriate. Categorical variables are summarized as absolute frequency (percentage). Group differences were tested using unpaired t test, Mann–Whitney U test or Wilcoxon matched pair signed rank test. Spearman’s rank correlation coefficient was used to assess statistical dependence. Association between categorical variables was tested using Chi-squared test or Fisher’s exact test as appropriate. A p < 0.05 was considered significant. A multivariable regression analysis was then performed to identify the independent association with EiPAH. All variables significantly associated with the relevant outcome at baseline were included in the multivariable model. Cumulative rates of the primary or secondary endpoints were calculated by using the Kaplan–Meier survival analysis, and the log-rank test was used for comparison across the groups.

**Results**

**General cardiopulmonary test and echocardiographic results**

CPET results for the 182 HCM patients are summarized in Table 1. On average, they presented a reduced exercise tolerance with a median VO2 peak 67% [57–67%]. Mean test duration was 9 ± 3 min, with mean peak exercise reaching 90 Watts. Mean RER was 1.1 ± 0.1, with only 17 patients (9%) showing a RER < 1; median VE/VCO2 slope was 27 [24–29]. The AT was reached in median at 55% of predicted peak VO2. The blood pressure response was normal in the majority of patients, hypertensive and flat respectively in 6 and 2 patients (3% and 1%). No arrhythmias were recorded during exercise. Stress test was terminated because of exhaustion and/or dyspnea. There were no complications during the tests.

Echocardiographic characteristics are summarized in Table 1. Most notably, 129 (71%) subjects had some degree of diastolic dysfunction at baseline, with 55 (30%) having a moderate-to-severe dysfunction (grade II/III). At peak exercise, 153 (84%) subjects had evidence of diastolic dysfunction. Median baseline sPAP was 20 mmHg [20–25 mmHg], while at peak exercise median sPAP was 25.5 mmHg [25–35 mmHg]. Eighty-two patients (44%) presented LVOT obstruction (ΔP ≥ 30 mmHg), which was present at rest in 41 patients and provokable in the remaining 41.

**Prevalence and correlation of EiPAH with clinical and CPET/echocardiography parameters**

Of the 182 study patients, 37 (20%) developed sPAP > 40 mmHg at peak exercise and therefore were considered to have EiPAH. Patients with EiPAH were more often females and were more likely to have LVOT obstruction (median peak LVOT gradient: 68 mmHg [20–100 mmHg] p < 0.001) than the 145 without EiPAH. Although a significant difference in terms of peak VO2 was not observed between the two patient groups, overall exercise performance was worse in EiPAH subjects in terms of peak Watts (70 Watts vs 100 Watts, p = 0.006) and exercise duration (8 ± 3 min vs 10 ± 3 min, p = 0.001) (Table 1). EiPAH was associated with higher VE/VCO2 slope (28 [25–32] vs 26 [22–29], p = 0.005). (Fig. 2) larger left atrial volume index (LAVI) (37 ± 14 ml/m2 vs 30 ± 12 ml/m2 p = 0.003) and higher prevalence of moderate-to-severe or severe mitral regurgitation (p < 0.001). Furthermore, EiPAH patients had a higher baseline sPAP with respect to non EiPAH (30 [25–35] vs 20 [19–22], p < 0.001)
| Parameter                              | Study population (n = 182) | EiPAH (n = 37) | No EiPAH (n = 145) | P value |
|----------------------------------------|---------------------------|---------------|-------------------|---------|
| Age                                    | 47.5 ± 15.9               | 48.0 ± 15.9   | 47.4 ± 13.8       | 0.809   |
| Females, n (%)                         | 64 (35.2)                 | 20 (54.1)     | 44 (30.3)         | 0.007   |
| BMI (kg/m²)                            | 25.9 ± 4.2                | 25.9 ± 3.9    | 25.9 ± 4.2        | 0.995   |
| NYHA classification, n (%)             |                           |               |                   | 0.466   |
| Grade I                                | 122 (67)                  | 24 (64.9)     | 98 (67.6)         |         |
| Grade II                               | 52 (28.6)                 | 10 (27)       | 42 (29)           |         |
| Grade III                              | 8 (4.4)                   | 3 (8.1)       | 5 (3.4)           |         |
| Grade IV                               | 0 (0)                     | 0 (0)         | 0 (0)             |         |
| B-Blockers, n (%)                      | 86 (60)                   | 16 (39)       | 70 (47)           | 0.40    |
| ACEi, n (%)                            | 21 (12)                   | 6 (15)        | 15 (10)           | 0.43    |
| Max LV thickness (mm)                  | 20.88 ± 4.7               | 20.76 ± 5     | 21 ± 4.4          | 0.31    |
| sPAP (mmHg)                            | 20 [19–24]                | 30 [25–35]    | 20 [19–22]        | < 0.001 |
| Baseline TAPSE (mm)                    | 21.4 ± 4.3                | 22.1 ± 5.4    | 21.2 ± 3.9        | 0.29    |
| Peak sPAP (mmHg)                       | 25.5 [25–35]              | 45 [40–49]    | 25 [25–30]        | < 0.001 |
| Peak TAPSE (mm)                        | 25.8 ± 4.5                | 26.6 ± 5      | 25.6 ± 4.3        | 0.281   |
| LVEF (%)                               | 67.1 ± 7.6                | 64.5 ± 7.6    | 67.8 ± 7.4        | 0.019   |
| Rest LVOT obstruction, n (%)           | 41 (22.2)                 | 20 (52.6)     | 21 (14.3)         | < 0.001 |
| Peak LVOT obstruction, n (%)           | 82 (44.3)                 | 28 (73.7)     | 54 (36.7)         | < 0.001 |
| Baseline LVOT gradient (mmHg)          | 10 [3.7–24]               | 27 [10–50]    | 10 [7–18]         | < 0.001 |
| Peak LVOT gradient (mmHg)              | 25 [16–60]                | 68 [20–100]   | 22 [15–47]        | < 0.001 |
| LAVi (ml/m²)                           | 31 ± 12                   | 37 ± 14       | 30 ± 12           | 0.003   |
| LAVi ≥ 34 ml/m², n (%)                 | 59 (33)                   | 40 (28.2)     | 19 (51.4)         | 0.008   |
| Baseline mean E/e¹                      | 11.6 ± 5                  | 14 ± 6.6      | 10.9 ± 4.3        | 0.001   |
| Peak mean E/e¹                         | 11.3 ± 4                  | 14 ± 4.2      | 10.6 ± 3.7        | < 0.001 |
| Baseline diastolic dysfunction, n (%)  |                           |               |                   | 0.008   |
| None                                   | 53 (29.1)                 | 8 (21.6)      | 45 (31)           |         |
| Grade I                                | 74 (40.7)                 | 10 (27)       | 64 (44.1)         |         |
| Grade II                               | 32 (17.6)                 | 9 (24.3)      | 23 (15.9)         |         |
| Grade III                              | 23 (12.6)                 | 10 (27)       | 13 (9)            |         |
| Peak diastolic dysfunction, n (%)      |                           |               |                   | 0.039   |
| None                                   | 29 (15.9)                 | 5 (13.5)      | 24 (16.6)         |         |
| Grade I                                | 73 (40.1)                 | 10 (27)       | 63 (43.4)         |         |
| Grade II                               | 52 (28.6)                 | 11 (29.7)     | 41 (28.3)         |         |
| Grade III                              | 28 (15.4)                 | 11 (29.7)     | 17 (11.7)         |         |
| Significant MR, n (%)                  | 13 (7)                    | 9 (24)        | 4 (2.7)           | < 0.001 |
| Baseline SBP (mmHg)                    | 125 ± 17                  | 125 ± 17      | 125 ± 17          | 0.577   |
| Peak SBP (mmHg)                        | 171 ± 29                  | 164 ± 31      | 173 ± 28          | 0.069   |
| RER                                    | 1.1 ± 0.11                | 1.10 ± 0.11   | 1.09 ± 0.11       | 0.501   |
| Baseline HR                            | 74 ± 14                   | 70 ± 14       | 75 ± 13           | 0.056   |
| Peak HR                                | 125 ± 23                  | 120 ± 24      | 127 ± 22          | 0.144   |
| HR reserve (%)                         | 0.64 ± 0.31               | 0.59 ± 0.23   | 0.66 ± 0.33       | 0.249   |
| Watt                                   | 90 [70–120]               | 70 [60–100]   | 100 [80–120]      | 0.006   |
| Exercise duration (min)                | 9 ± 3                     | 8 ± 3         | 10 ± 3            | 0.001   |
| Peak VO₂ (ml/kg/min)                   | 19 [3, 15–22]             | 17 [3, 14–21] | 19 [3, 15–22]     | 0.094   |
| Peak VO₂ (%)                           | 67 [57–76]                | 67.5 [51.75 76.25] | 67 [57.5 – 75.5] | 0.867   |
| HR/VO₂ (BPM/ml)                        | 12.9 ± 4.1                | 12 ± 4.1      | 13.2 ± 4.1        | 0.269   |
| AT                                     | 53 ± 18                   | 52 ± 19       | 54 ± 17           | 0.85    |
| VE/VCO₂                                | 27 [24–29]                | 28 [25–32]    | 26 [22.2–29]      | 0.005   |
(Table 1). Of the baseline echocardiographic characteristics and CPET parameters associated with EiPAH at univariate analysis (in particular LVOT gradient, VE/VCO₂ slope, maximum Watts, baseline sPAP, LAVi and degree of diastolic dysfunction) only baseline sPAP (p < 0.0001) and baseline LVOT obstruction (p = 0.028) were significantly associated with the development of EiPAH in a multivariable model (Table 2).

### Outcome

Median follow up duration was 6.5 years (IQR 5–7.8). The composite primary endpoint occurred in 8 (4.4%) patients during this time, while the secondary endpoint occurred in 30 (16.5%) (Table 3). During follow up EiPAH was significantly associated with cardiovascular

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**Table 2** Univariate and multivariate logistic regression analysis to identify independent predictors of exercise induced pulmonary artery hypertension

| Variable                  | Univariate analysis |          |                 |                  | Multivariate logistic regression |          |
|---------------------------|--------------------|----------|-----------------|------------------|-------------------------------|----------|
|                           | OR (95% CI)        | p value  | OR (95% CI)     | p value          |                               |          |
| Female                    | 2.70 (1.29–5.64)   | 0.008    | 2.70 (1.29–5.64) | 0.008            |                               |          |
| VE/VCO₂                   | 1.08 (1.01–1.15)   | 0.016    | 1.08 (1.01–1.15) | 0.016            |                               |          |
| LAVi                      | 1.04 (1.01–1.07)   | 0.005    | 1.04 (1.01–1.07) | 0.005            |                               |          |
| Maximum Watts             | 0.98 (0.97–0.99)   | 0.019    | 0.98 (0.97–0.99) | 0.019            |                               |          |
| Baseline sPAP             | 1.37 (1.24–1.51)   | <0.001   | 1.37 (1.24–1.51) | <0.001           |                               |          |
| Baseline mean E′/E′       | 1.11 (1.04–1.19)   | 0.002    | 1.11 (1.04–1.19) | 0.002            |                               |          |
| Baseline LVOT gradient    | 1.04 (1.02–1.06)   | <0.001   | 1.04 (1.02–1.06) | <0.001           |                               |          |

Hosmer e Lemeshow test p = 0.065; AUC = 86 (95% CI 77–95); Nagelkerke R² = 53.1%

LAVi left atrium volume index; LVOT left ventricle outflow tract; VE/VCO₂ ventilation/carbon dioxide slope; sPAP systolic pulmonary arterial pressure
and non-cardiovascular mortality (0.7% vs 8% and 0.7% vs 10.8%; \( p < 0.001 \)), HF hospitalization (2% vs 13.5%; \( p < 0.001 \)) and with AF (6.2% vs 21.6%; \( p < 0.001 \)). After adjustment for age and sex, EiPAH was significantly associated with the occurrence of primary and secondary endpoints (Fig. 1). Multivariable Hazard Ratio (HR) was 6.21 (95% confidence interval 1.47–26.19, \( p = 0.05 \)) for the primary and 4.21 (95%CI 1.94–9.12, \( p < 0.001 \)) for the secondary endpoint.

## Discussion

The present study assessed the prevalence and clinical significance of PAH occurring in response to exercise in a consecutive cohort of 182 HCM patients. The main findings can be summarized as follows: (1) after excluding patients with baseline sPAP > 36 mmHg (i.e. with resting PAH), one out of five HCM patients with normal estimated pulmonary pressures at rest developed EiPAH; (2) clinical predictors of EiPAH included higher baseline sPAP values and baseline LVOT gradient; EiPAH patients were also more likely to have left atrial dilatation and diastolic dysfunction. (3) EiPAH was associated with impaired functional capacity and predicted adverse outcome, defined by a composite endpoint including all-cause death, heart transplantation, aborted sudden cardiac death, nonfatal myocardial infarction, nonfatal stroke or hospitalization for decompensated HF. The primary endpoint of the study (all-cause death, heart transplantation or aborted sudden cardiac death) was not met, likely due to the paucity of events. Overall, these findings are consistent with—but expand the significance of—prior reports limited to resting PAH in both obstructive and non-obstructive HCM patients, showing a close association with diastolic dysfunction, LVOT obstruction and mitral regurgitation [3]. Conversely, they are at odds with the study by Hatamami et al [13] in which the degree of mitral regurgitation and LVOT obstruction did not correlate with EiPAH, probably due to an older study population with milder obstructive profile. The novel concept emerging from our study, however, is that static evaluation of hemodynamic balance at rest will substantially underestimate clinical frailty associated with provokable PAH. In the light of our findings, exercise echocardiography coupled with CPET represents an invaluable test to uncover early stages of PAH suggesting pending decompensation.

The mechanisms by which EiPAH develops in HCM remain incompletely understood. Over time diastolic...
dysfunction and mitral regurgitation due to SAM result in adverse atrial remodeling as elevated left ventricular and atrial pressures are passively transmitted to the pulmonary vasculature. Moreover, LVOT obstruction increases afterload, contributing to elevated left ventricular pressures. Ultimately, structural changes in the pulmonary vasculature of HCM patients may develop from long-standing elevations in left atrial pressures, as seen in other forms of post-capillary PAH [19]. Hence, dynamic assessment provided by exercise echo, combined with cardiopulmonary test, represents the most comprehensive approach to elucidate the individual pathophysiological determinants of functional intolerance in HCM patients [20].

The importance of identifying EiPAH has been increasingly recognized in view of its prognostic role and therapeutic implications in several CV diseases [21, 22]. We have now shown this to be the case also in HCM, consistent with a previous study in which EiPAH was an independent predictor of HCM related morbidity [13]. The only other metabolic indicator associated with HCM was VE/VCO2, a parameter whose importance has already been emphasized in conditions characterized by diastolic dysfunction (i.e. HfPEF) resulting in impaired exercise tolerance, largely due to increased myocardial stiffness with retrograde increase in pulmonary pressures. As a consequence, an elevated VE/VCO2 slope should be considered a red flag reflecting the mismatch between pulmonary ventilation and pulmonary perfusion [22].

The present results have clinical implications: HCM patients with normal estimated sPAP at rest should be routinely assessed, particularly when active and complaining of symptoms that cannot be readily explained by instrumental evaluation at rest. The combination of CPET and exercise echocardiography represents the gold standard of functional assessment in this disease, by allowing the simultaneous evaluation of LVOT gradients, diastolic reserve, mitral regurgitation, and pulmonary pressures during various phases of exercise and recovery, as well as VO2 and VE/VCO2 slope. Nevertheless, in a subset of patients with EiPAH a further invasive investigation might be necessary to distinguish a pure post-capillary mechanism from a combination of pre- and post-capillary components (6). In any case, all patients with EiPAH should be considered for a closer clinical surveillance in order to optimize pharmacological treatment, plan invasive management when appropriate and prevent disease progression. Conversely, patients who maintain normal sPAP on exercise appear to be at low mid-term risk of heart failure-related events and adverse outcome. Although only a small minority of HCM centers perform simultaneous CPET and exercise echocardiography, such practice should be encouraged in the light of the wealth of information obtainable in individual patients [23, 24]. Ideally, serial evaluations over time may increase predictive accuracy: this hypothesis needs systematic assessment in the future.

Limitations

This was a single-center study, and its interpretation cannot be applied by default to the whole HCM population. The study used echocardiographic estimates of pulmonary pressures: as no invasive measure was obtained, we could not exclude PAH be due to a primary change in pulmonary vascular resistance. Nevertheless, such occurrence appears unlikely in HCM patients, and good agreement between echocardiographic and invasive measures of pulmonary pressures during upright exercise has already been shown among patients with high quality tricuspid Doppler signal [25].

Conclusions

EiPAH was present in about one fifth of HCM patients without evidence of elevated pulmonary pressures at rest and was associated with adverse clinical outcome. Diagnosing EiPAH by exercise echo/CPET may help physicians to detect early stage of PAH requiring a closer clinical monitoring and individualized treatment strategies.

Author contributions FR, MB and IO conceived the idea presented, wrote the manuscript and supervised the work. GH and FM contributed to the acquisition, analysis, and interpretation of data for the work. PB collected figures and tables and performed the literature research. AA and EZ critically revised the manuscript. All authors contributed to the editorial changes in the manuscript. All authors read and approved the final manuscript.

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Declarations

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Informed consent All patients provided written informed consent.

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