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ORIGINAL PAPER

# Prevalence, determinants, and prognostic significance of exercise-induced pulmonary hypertension in patients with hypertrophic cardiomyopathy

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## Abstract

Exercise-induced pulmonary hypertension (EIPH) is associated with worse outcomes in patients with heart failure or valvular heart disease. However, little is known regarding the implications of EIPH in hypertrophic cardiomyopathy (HCM) patients. We retrospectively reviewed data of consecutive HCM patients who underwent clinically indicated exercise echocardiography using a semi-supine bicycle ergometer at our hospital. EIPH was defined as pulmonary artery systolic pressure ≥ 60 mmHg during exercise. The incidences of HCM-related mortality and HCM-related morbidity during follow-up period were evaluated. Of 42 patients (mean age 59 ± 21 years; 4 with resting obstruction, 19 with provoked obstruction, and 19 without obstruction), 16 (38%) developed EIPH. Patients with EIPH had significantly longer resting E wave deceleration time (271 ± 116 vs. 213 ± 66 ms; $P = 0.04$), higher resting pulmonary artery systolic pressure (35 ± 6 vs. 31 ± 5 mmHg; $P = 0.04$), and higher B-type natriuretic peptide level (283 [222, 465] vs. 142 [54, 423] pg/ml; $P = 0.04$) than those without EIPH. Kaplan–Meier curve analysis demonstrated that EIPH was significantly associated with HCM-related morbidity (log-rank; $P = 0.01$). In Cox regression analysis, EIPH was a significant predictor of HCM-related morbidity (hazard ratio: 5.98, 95% confidence interval 1.36–41.07; $P = 0.02$). In conclusion, EIPH was documented in about one-third of HCM patients. EIPH was a significant predictor of HCM-related morbidity in patients with HCM.

**Keywords** Exercise-induced pulmonary hypertension · Hypertrophic cardiomyopathy · Exercise echocardiography

## Introduction

Pulmonary hypertension (PH), defined as an increase in mean pulmonary arterial pressure ≥ 25 mmHg at rest [1], is a known complication of cardiac diseases and exerts a negative impact on clinical outcomes [2]. Exercise stresses the cardiac and pulmonary circulation, and exercise-induced PH (EIPH) may occur even in patients without resting PH. EIPH is also reported to be associated with worse clinical outcomes in heart failure (HF) with reduced ejection fraction [3], HF with preserved ejection fraction [4], mitral regurgitation [5, 6], and aortic stenosis [7].

Hypertrophic cardiomyopathy (HCM) is the most common heritable cardiac disease. PH and/or EIPH may also develop in HCM patients. Recently, several studies have addressed the prevalence, determinants, and prognostic significance of PH in patients with HCM [8–12]. However, little is known regarding the implications of EIPH in HCM patients.

Accordingly, the aim of this study was to investigate the prevalence, determinants, and prognostic significance of EIPH in patients with HCM using the data of exercise echocardiography.

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## Methods

### Study population

We retrospectively reviewed data of patients with HCM who underwent clinically indicated exercise echocardiography in a Japanese referral hospital. The diagnosis of HCM was made by cardiologists experienced in this disease. In this study, we excluded patients with end-stage HCM (defined as left ventricular [LV] ejection fraction < 50%), severe (grade 4 +) valvular heart disease, congenital heart disease, severe lung disease and pulmonary arterial hypertension, and those in whom we could not obtain data about pulmonary artery systolic pressure (PASP) during exercise. Clinical backgrounds obtained at the time of exercise echocardiography were collected from electronic medical records. All patients signed statements agreeing to the use of their medical information for research. This study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center (M30-023), and conducted according to the Declaration of Helsinki.

### Resting and stress echocardiography

All patients underwent comprehensive resting echocardiography according to guidelines [13]. LV obstruction was measured by continuous-wave Doppler echocardiography. Valsalva maneuver was used to provoke the LV pressure gradient. Resting obstruction was defined as LV obstruction ≥ 30 mmHg at rest, provoked obstruction as resting gradient < 30 mmHg but provoked gradient (under Valsalva maneuver or exercise) ≥ 30 mmHg, and without obstruction as both resting and provoked gradient < 30 mmHg [14, 15]. The morphology of LV hypertrophy was classified as asymmetrical septal hypertrophy, apical hypertrophy and other forms [16]. The degree of mitral regurgitation was graded as follows: 0 = none, 1 + = mild, 2 + = moderate, 3 + = moderately severe, and 4 + = severe. PASP was estimated from the maximal velocity of the tricuspid regurgitant jet using continuous-wave Doppler with the simplified Bernoulli equation and adding the right atrial pressure, which was assumed to be 10 mmHg [3, 17]. EIPH was defined as peak PASP with exercise ≥ 60 mmHg according to previous studies [3, 5–7]. Exercise echocardiography was conducted in accordance with guideline recommendations [18–20]. Exercise consisted of bicycle exertion in a semi-supine position with a slight left lateral tilt, on a tilting bicycle ergometer (ergometer and tilt table 750EC; Lode). Workload was increased by 25 W every 2 min, up to the maximum tolerated effort. At each stage from rest to recovery, conventional echocardiographic recordings, 12-lead electrocardiogram and vital signs were acquired. Exercise endpoints included significant arrhythmia, severe hypertension (systolic blood pressure > 240 mmHg or diastolic blood pressure > 110 mmHg), hypotensive response, or limiting symptom.

### Study endpoints

In order to estimate the impact of EIPH on prognosis in HCM patients, two specific endpoints were evaluated. HCM-related mortality was defined as composite of cardiovascular death, heart transplantation and/or LV assist device implantation. HCM-related morbidity was defined as the composite of sustained ventricular tachycardia, hospitalization due to HF, and atrial fibrillation (AF) events (new-onset AF or hospitalization due to AF such as cardioversion).

### Statistics

Continuous variables are presented as mean ± standard deviation when normally distributed, and as median and interquartile range when non-normally distributed. Comparison of differences among groups was performed using unpaired Student's *t* test or Mann–Whitney U test for continuous variables, and chi-squared test or Fisher's exact test for dichotomous variables, when appropriate. First, we divided the patients into two groups according to the presence or absence of EIPH, and compared the clinical background and echocardiographic parameters between patients with and without EIPH. The optimal cut-off value for the determinants of EIPH was calculated by receiver-operating characteristics curve analysis. Second, Kaplan–Meier survival plots were constructed by dividing the subjects by presence or absence of EIPH, and log-rank testing was performed. Cox regression analysis was performed to evaluate the prognostic significance of EIPH. All tests were 2 tailed, and a value of $P < 0.05$ was considered statistically significant. All analyses were performed with JMP version 10 (SAS Institute, Cary, NC).

## Results

### Study population

A total of 62 patients with HCM who underwent clinically indicated exercise echocardiography were screened. Of these 62 patients, we excluded 17 patients (27%) in whom we could not obtain PASP during exercise. We also excluded 3 patients with end-stage HCM. Finally, we enrolled 42 patients (mean age 59 ± 21 years, mean LV ejection fraction: 61 ± 6%; 4 with resting obstruction, 19 with provoked

obstruction, and 19 without obstruction) in this study. We included 36 patients with asymmetrical septal hypertrophy, 4 with apical hypertrophy, and 2 with other morphology of LV hypertrophy. The distribution of peak PASP with exercise is shown in Fig. 1a. Of 42 patients, 16 patients (38%) developed EIPH during exercise. The prevalence of EIPH did not differ between HCM phenotypes ($P=0.36$) (Fig. 1b).

### Clinical profile of HCM patients with and without EIPH

The clinical profiles of HCM patients with and without EIPH are shown in Table 1. Patients with EIPH had significantly higher B-type natriuretic peptide level ($P=0.04$), longer E wave deceleration time at rest ($P=0.04$) and higher resting PASP ($P=0.04$), compared with those without EIPH. The optimal cut-off value of B-type natriuretic peptide level for the development of EIPH was 222 pg/ml, that of E wave deceleration time was 330 ms, and that of resting PASP was 35 mmHg. B-type natriuretic peptide, E wave deceleration time and resting PASP had modest discriminative ability for the determinants of EIPH (area under the curve: 0.69, 0.63 and 0.75; respectively). Other backgrounds and echocardiographic variables, including LV obstruction and mitral regurgitation at rest or with exercise, were comparable between the two groups.

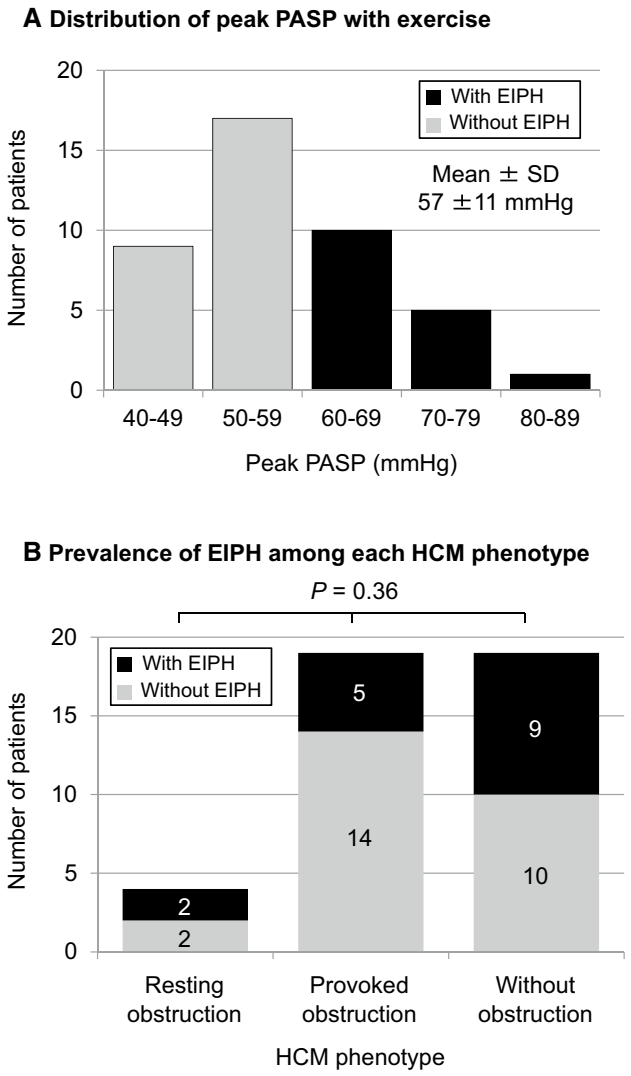


**Fig. 1** **a** Distribution of peak PASP with exercise. **b** Prevalence of EIPH among each HCM phenotype. *EIPH* exercise-induced pulmonary hypertension, *HCM* hypertrophic cardiomyopathy, *PASP* pulmonary artery systolic pressure, *SD* standard deviation

### Prognostic significance of EIPH in HCM patients

During a median follow-up period of 730 days (interquartile range 379 to 1334 days), HCM-related mortality occurred in 1 case (LV assist device implantation), and HCM-related morbidity occurred in 8 cases (sustained ventricular tachycardia: 2, hospitalization due to HF: 2 and AF event: 4 [new-onset AF: 3, hospitalization for cardioversion: 1]). Patients with EIPH had 2 hospitalizations due to HF and 4 AF events, whereas those without EIPH had 1 HCM-related mortality and 2 sustained ventricular tachycardia events. Kaplan–Meier curve analysis demonstrated that EIPH was not associated with the incidence of HCM-related mortality (log-rank; $P=0.45$). Meanwhile, patients with EIPH had a significantly higher incidence of HCM-related morbidity than those without EIPH during the follow-up period (log-rank; $P=0.01$) (Fig. 2). In univariable Cox regression analysis, EIPH was significantly associated with increased risk of HCM-related morbidity ($P=0.02$), but not PASP at rest (Table 2).

## Discussion

Our study provided an estimate of the prevalence and determinants of EIPH and its prognostic significance in a cohort of consecutive HCM patients who underwent clinically indicated exercise echocardiography. Our findings suggested that EIPH was an important prognostic parameter in patients with HCM.

### Prevalence of EIPH in HCM patients

There is a paucity of literature assessing the prevalence of EIPH in HCM patients. Our study demonstrated that EIPH was present in about one-third of HCM patients who underwent exercise echocardiography. The prevalence of EIPH in our HCM cohort is consistent with values reported in valvular heart disease patients [21, 22]. Although invasive right heart catheterization remains the gold standard for assessment of pulmonary artery pressure, catheterization with

**Table 1** Baseline characteristics of hypertrophic cardiomyopathy patients with and without EIPH

| | Total n = 42 | With EIPH n = 16 | Without EIPH n = 26 | *P* value |
|---|---|---|---|---|
| Backgrounds | | | | |
| Age (years) | 59 ± 21 | 62 ± 21 | 57 ± 20 | 0.50 |
| Male | 14 (33%) | 4 (25%) | 10 (38%) | 0.89 |
| New York Heart Association class I | 8 (19%) | 2 (13%) | 6 (23%) | 0.68 |
| History of atrial fibrillation | 6 (14%) | 4 (25%) | 2 (8%) | 0.18 |
| Non-sustained ventricular tachycardia | 8 (19%) | 2 (13%) | 6 (23%) | 0.69 |
| Pacemaker/defibrillator | 9 (21%) | 3 (19%) | 6 (23%) | 1.00 |
| B-type natriuretic peptide (pg/ml) | 222 (100, 451) | 283 (222, 465) | 142 (54, 423) | 0.04 |
| Beta-blocker | 27 (64%) | 10 (63%) | 17 (65%) | 0.85 |
| Calcium channel blocker | 5 (12%) | 3 (19%) | 2 (8%) | 0.35 |
| Disopyramide/cibenzoline | 13 (31%) | 5 (31%) | 8 (31%) | 0.97 |
| Exercise measurements | | | | |
| Systolic blood pressure at rest (mmHg) | 128 ± 23 | 123 ± 17 | 132 ± 25 | 0.20 |
| Systolic blood pressure with exercise (mmHg) | 167 ± 33 | 163 ± 32 | 169 ± 34 | 0.53 |
| Heart rate at rest (beats/min) | 64 ± 10 | 63 ± 9 | 64 ± 11 | 0.84 |
| Heart rate with exercise (beats/min) | 112 ± 22 | 115 ± 19 | 110 ± 24 | 0.51 |
| Maximum workload (W) | 83 ± 31 | 71 ± 25 | 90 ± 33 | 0.06 |
| Morphology of LV hypertrophy | | | | |
| Asymmetrical septal hypertrophy | 36 (85%) | 13 (81%) | 23 (88%) | |
| Apical hypertrophy | 4 (10%) | 3 (19%) | 1 (4%) | 0.17 |
| Others | 2 (5%) | 0 (0%) | 2 (8%) | |
| Echocardiographic parameters | | | | |
| LV end-diastolic dimension (mm) | 42 ± 5 | 42 ± 7 | 42 ± 6 | 0.93 |
| LV ejection fraction (%) | 61 ± 6 | 60 ± 5 | 61 ± 6 | 0.70 |
| Maximum LV wall thickness (mm) | 18 ± 4 | 18 ± 5 | 18 ± 4 | 0.61 |
| LV wall mass index ($g/m^2$) | 155 ± 54 | 161 ± 47 | 151 ± 59 | 0.55 |
| Left atrial diameter (mm) | 42 ± 8 | 44 ± 8 | 41 ± 7 | 0.18 |
| Left atrial volume index ($ml/m^2$) | 51 ± 17 | 52 ± 19 | 50 ± 17 | 0.79 |
| E wave (cm) | 70 ± 26 | 64 ± 26 | 73 ± 27 | 0.29 |
| A wave (cm) | 70 ± 25 | 68 ± 27 | 71 ± 25 | 0.68 |
| E/A ratio | 0.9 (0.7, 1.4) | 1.0 (0.7, 1.4) | 0.9 (0.7, 1.4) | 0.77 |
| E wave deceleration time (ms) | 235 ± 92 | 271 ± 116 | 213 ± 66 | 0.04 |
| e′ (septal) (cm/s) | 3.8 (2.4, 5.3) | 3.5 (2.1, 5.8) | 4.5 (2.9, 5.3) | 0.39 |
| e′ (lateral) (cm/s) | 5.7 (4.3, 7.5) | 4.9 (4.2, 8.3) | 5.8 (4.1, 7.4) | 0.52 |
| E/e′ (average) | 15.1 ± 5.7 | 14.5 ± 5.8 | 15.5 ± 5.7 | 0.60 |
| LV gradient at rest (mmHg) | 10 (5, 18) | 10 (4, 21) | 10 (5, 17) | 0.91 |
| LV gradient at rest ≥ 30 mmHg | 4 (10%) | 2 (13%) | 2 (7%) | 0.63 |
| LV gradient with exercise (mmHg) | 29 (12, 62) | 24 (11, 54) | 31 (13, 74) | 0.50 |
| LV gradient with exercise ≥ 30 mmHg | 20 (48%) | 6 (38%) | 14 (54%) | 0.30 |
| Provoked LV gradient (exercise and/or Valsalva) ≥ 30 mmHg | 23 (55%) | 7 (44%) | 16 (62%) | 0.26 |
| PASP at rest (mmHg) | 33 ± 6 | 35 ± 6 | 31 ± 5 | 0.04 |
| PASP at rest ≥ 40 mmHg | 6 (15%) | 4 (25%) | 2 (8%) | 0.18 |
| Mitral regurgitation ≥ grade 2 + at rest | 7 (17%) | 2 (13%) | 5 (19%) | 0.69 |
| Mitral regurgitation ≥ grade 2 + with exercise | 15 (36%) | 5 (31%) | 10 (39%) | 0.64 |

Continuous variables are presented as mean ± standard deviation if normally distributed, and median (interquartile range) if not normally distributed. Categorical variables are presented as number of patients (%)

*EIPH* exercise-induced pulmonary hypertension, *LV* left ventricular, *PASP* pulmonary artery systolic pressure

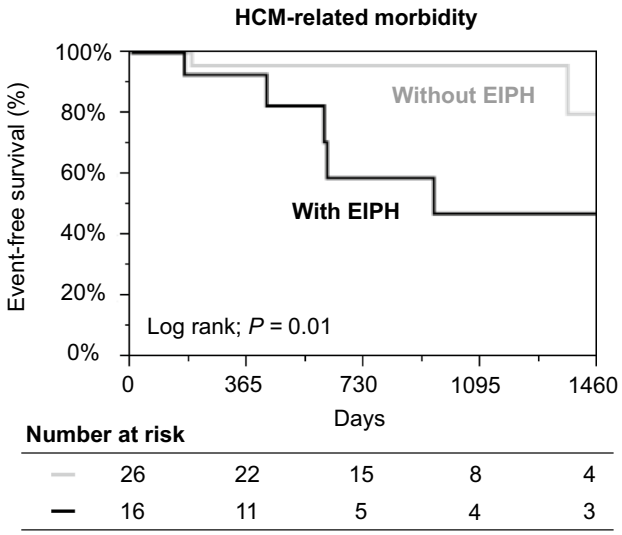


**Fig. 2** Kaplan–Meier analysis for HCM-related morbidity in HCM patients with and without EIPH. *EIPH* exercise-induced pulmonary hypertension

exercise is not commonly used because of limited exercise load and possible complications. Exercise echocardiography can be performed non-invasively and repeatedly with sufficient exercise load. Therefore, we believe that data about EIPH derived from exercise echocardiography have certain value in relation to HCM patients in clinical practice.

## Determinants of EIPH in HCM patients

PH may develop in HCM patients due to elevated LV filling pressure secondary to diastolic dysfunction, LV obstruction, or mitral regurgitation. Meanwhile, the mechanisms by which EIPH develops in HCM patients remain incompletely elucidated. Our study demonstrated that patients with EIPH had higher resting PASP, longer E wave deceleration time at rest, and higher B-type natriuretic peptide level. Elevated resting PASP might be the consequence of increase in LV filling pressure, and peak velocity of tricuspid regurgitation jet is suggested for the evaluation of diastolic dysfunction in HCM patients [23, 24]. The increase in resting PASP was subtle in our cohort, but exercise could unmask the change in PASP. Concerning E wave deceleration time, interpretation of this result needs care, because it has been reported that conventional Doppler parameters including E wave deceleration time do not accurately correlate with LV filling pressure in HCM patients [25]. However, several studies reported that E wave deceleration time could be a marker of impaired relaxation in HCM patients [26–28]. Actually, a recent study of EIPH in HF with preserved ejection fraction demonstrated that patients with EIPH had longer E wave deceleration time and higher N-terminal pro B-type natriuretic peptide level, as was the case in our study, and concluded that patients with EIPH had worse diastolic dysfunction [17]. Although speculative, EIPH in HCM patients might represent intrinsic diastolic dysfunction, and exercise can unmask it in HCM patients.

On the contrary, we found only an inconsistent relation between EIPH and mitral regurgitation and/or LV obstruction at rest or with exercise. In our cohort, the number of mitral regurgitation ≥ grade 3 + was only 1 patients (2%) at rest and 4 patients (10%) with exercise, limiting the ability to investigate the association between mitral regurgitation and EIPH. With regard to LV obstruction, previous studies reported that resting PH was not associated with the degree of LV obstruction [8, 10], which were consistent with our findings. However, the potential contribution of LV obstruction to the development of EIPH remains incompletely resolved and needs to be clarified by further studies. Furthermore, a previous study raised the possibility of coexistent

**Table 2** Cox proportional hazard analysis for the determinants of HCM-related morbidity

| | Hazard ratio (95% CI) | *P* value |
|---|---|---|
| LV end-diastolic dimension (/1 mm) | 1.02 (0.87–1.18) | 0.83 |
| LV ejection fraction (/1%) | 0.85 (0.70-0.999) | 0.049 |
| LV wall mass index (/1 g/m$^2$) | 1.01 (0.99–1.02) | 0.09 |
| Left atrial volume index (/1 ml/m$^2$) | 1.01 (0.96–1.06) | 0.69 |
| E wave deceleration time (/1 ms) | 1.00 (0.99–1.01) | 0.82 |
| E/e′ (average) (/1 unit) | 1.00 (0.88–1.13) | 0.95 |
| LV gradient at rest ≥ 30 mmHg | 1.93 (0.10-13.09) | 0.58 |
| Provoked LV gradient (exercise and/or Valsalva) ≥ 30 mmHg | 1.03 (0.25–5.13) | 0.97 |
| Pulmonary artery systolic pressure at rest (/1 mmHg) | 1.06 (0.96–1.18) | 0.28 |
| Pulmonary artery systolic pressure ≥ 40 mmHg | 0.91 (0.13–4.30) | 0.92 |
| Exercise-induced pulmonary hypertension | 5.98 (1.36–41.07) | 0.02 |
| Mitral regurgitation ≥ grade 2 + at rest | 1.98 (0.27–10.33) | 0.45 |
| Mitral regurgitation ≥ grade 2 + with exercise | 0.66 (0.09–3.06) | 0.61 |

*CI* confidence interval, *LV* left ventricular

intrinsic pulmonary vascular disease in some HCM patients with resting PH [8]. EIPH was reported to be caused not only by the exercise-induced increase in left atrial pressure but also by the exercise-induced pulmonary vasoconstriction [29, 30]. Therefore, further studies are strongly warranted to investigate the mechanisms of EIPH in patients with HCM.

### Prognostic significance of EIPH in HCM patients

Ventricular tachycardia is a devastating morbidity in HCM patients. Besides, HF and AF have assumed an increasing morbidity in patients with HCM [31]. PH and/or EIPH appear to be the consequence of the increase of LV filling pressure, which could promote the occurrence of ventricular tachycardia. Moreover, increased LV filling pressure results in atrial overload and remodeling, which might promote the occurrence of HF and AF. Indeed, PH in HCM patients was significantly associated with increased morbidity [8–10]. Our results confirmed that EIPH also shows a significant association with HCM-related morbidity, perhaps because EIPH represents the downstream effect of the hemodynamic derangements that increase LV filling pressure during exercise. These findings are consistent with prior studies of other cardiac diseases in which EIPH was associated with worse clinical outcomes [5–7], thereby underscoring the potential value of EIPH in HCM patients as well. Although data about tailored therapy for PH and/or EIPH in HCM patients are lacking, our study suggests that HCM patients with EIPH should have close clinical follow-up to reduce the risk of hemodynamic worsening or instability and arrhythmias.

### Limitations

First, this study was a single-center retrospective study, so it was subject to various bias inherent in such data. The study population was small, resulting in a decrease in the statistical power of the study. We included only 4 patients (10%) with resting obstruction and we inevitably analyzed HCM phenotypes altogether. The low rate of events was also a major limitation of this study. Moreover, as a referral hospital, several patients do not receive longitudinal care and follow-up. Thus, our study is hypothesis-generating research, and larger studies with longer follow-up period are warranted. Second, HCM-related morbidity in this study was mainly driven by the AF events. Besides, new-onset AF events could have been missed in some patients, because patients were followed individually at the discretion of the attending physicians. Third, pulmonary hemodynamics was assessed by echocardiography and not right heart catheterization. Therefore, some patients (17/62 patients) with immeasurable tricuspid regurgitation jet velocity during exercise were excluded from this analysis. A high rate of exclusions was a critical limitation in this study. Fourth, right atrial pressure was estimated at 10 mmHg both at rest and during exercise, although this may vary among subjects. Nevertheless, the noninvasive evaluation of right atrial pressure during exercise remains difficult, is probably subject to low accuracy, and is not validated. Fifth, we did not obtain data about LV strain, right ventricular function, pressure gradient of pulmonary artery regurgitation, and acceleration time at right ventricular outflow tract at rest and with exercise. Moreover, cardiac magnetic resonance imaging data were not available for all patients in the present study. Thus, we could not investigate the correlation between these parameters and EIPH in patients with HCM.

## Conclusion

EIPH was documented in about one-third of HCM patients who underwent clinically indicated exercise echocardiography. E wave deceleration time, PASP at rest, and B-type natriuretic peptide level were associated with EIPH. EIPH was an independent predictor of HCM-related morbidity, suggesting the potential role of exercise echocardiography in HCM patients.

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### Compliance with ethical standards

**Conflict of interest** The authors declare that there is no conflict of interest.

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