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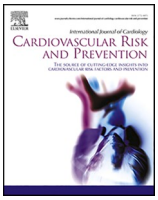

Prevalence and prognostic implications of hypertensive response to exercise in patients with hypertrophic cardiomyopathy☆

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ABSTRACT

Objective: Hypertensive response to exercise (HRE) is observed in patients with hypertrophic cardiomyopathy (HCM) with normal resting blood pressure (BP). However, the prevalence or prognostic implications of HRE in HCM remain unclear.

Methods: In this study, normotensive HCM subjects were enrolled. HRE was defined as systolic BP > 210 mmHg in men or >190 mmHg in women, or diastolic BP > 90 mmHg, or an increase in diastolic BP > 10 mmHg during treadmill exercise. All participants were followed for subsequent development of hypertension, atrial fibrillation (AF), heart failure (HF), sustained ventricular tachycardia/fibrillation (VT/VF), and all-cause death. Six hundred and eighty HCM patients were screened.

Results: 347 patients had baseline hypertension, and 333 patients were baseline normotensive. 132 (40%) of the 333 patients had HRE. HRE was associated with female sex, lower body mass index and milder left ventricular outflow tract obstruction. Exercise duration and metabolic equivalents were similar between patients with or without HRE, but the HRE group had higher peak heart rate (HR), better chronotropic response and more rapid HR recovery. Conversely, non-HRE patients were more likely to exhibit chronotropic incompetence and hypotensive response to exercise. After a mean follow-up of 3.4 years, patients with and without HRE had similar risks of progression to hypertension, AF, HF, sustained VT/VF or death.

Conclusion: HRE is common in normotensive HCM patients during exercise. HRE did not carry higher risks of future hypertension or cardiovascular adverse outcomes. Conversely, the absence of HRE was associated with chronotropic incompetence and hypotensive response to exercise.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disorder characterized by unexplained ventricular hypertrophy, myofibrillar disarray and myocardial fibrosis [1,2]. Clinical manifestations range from exercise intolerance, heart failure, cardiac arrhythmias or even sudden cardiac death. Across the age spectrum of HCM, hypertension is a common comorbid condition in approximately 30–50% of all HCM patients [3,4]. In HCM patients with normal rest blood pressure (BP), their BP may become markedly elevated during exercise. However, data about the prevalence of hypertensive response to exercise (HRE) in HCM are scarce. In addition, studies investigating HRE and associated cardiovascular risks showed conflicting results. Some publications reported HRE as a risk marker for the development of future hypertension and cardiovascular diseases [5,6], while others suggested that larger augmentations in blood pressure and heart rate during

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exercise were associated with lower risks of adverse cardiovascular (CV) events and death [7,8]. Therefore, in this study we aimed to ascertain the prevalence and determinants of HRE in HCM, and to investigate the association of HRE and progression to hypertension or other adverse CV events.

2. Methods

This study was approved by the Institutional Review Board and study participants signed informed consent for procedures performed for research purposes. Consecutive patients who initially presented to the Johns Hopkins HCM Center between 2005 and 2015 were enrolled, and a diagnosis of HCM was made based on standard published criteria, namely a non-dilated, hypertrophic left ventricle (≥15 mm) in the absence of other systemic causes capable of producing such magnitude of hypertrophy [9]. Patients were considered as hypertensive at baseline if they had history of hypertension and were on anti-hypertensive medications, or they had resting systolic blood pressure≧140 mmHg or diastolic blood pressure≧90 mmHg at index visit [10].

HCM patients with active angina, decompensated heart failure, uncontrolled arrhythmias, hemodynamic instability, severe hyper/hypotension and inability to walk on treadmill were excluded from examination (n = 25; 4%). Other patients without contraindications underwent symptom-limited treadmill exercise stress testing using a Bruce protocol except for those with a history of poor functional status, in which case a modified Bruce or Naughton protocol was applied. Patients were encouraged to exercise until they developed symptoms or fatigue which precluded continuation of exercise. Patients were on continuous 12-lead ECG monitoring and blood pressure was measured at every stage. The examination was terminated early in case of sustained ventricular arrhythmia, symptomatic drop in BP, ST elevation or development of severe symptoms. Ongoing medications were continued prior to stress testing [11].

HRE was defined either as peak systolic blood pressure (SBP) > 210 mmHg in men or > 190 mmHg in women, or as peak diastolic blood pressure (DBP) > 90 mmHg, or as an increase in DBP >10 mmHg during exercise [12]. Abnormal blood pressure response (ABPR) was defined as failure to increase systolic blood pressure by at least 20 mmHg, or as a drop in systolic blood pressure during exercise by > 20 mmHg from the peak value [9]. Target heart rate during exercise stress was set at 80% of maximal predicted heart rate. Rate-pressure product (RPP) was the product of maximal achieved SBP and heart rate during exercise [13]. HR recovery was defined as the difference in HR between peak exercise and 1-min rest after cessation [14]. Chronotropic response (CR) was calculated according to the formula: (peak HR – baseline HR)/(220 – age – baseline HR) x 100% [15,16]. A CR < 80% in a subject not receiving beta-blockers [17,18] or < 62% in a subject receiving beta-blockers was considered as chronotropic incompetence [19].

Transthoracic echocardiography was performed using a GE Vivid 7 or E−9 ultrasound machine (*GE Ultrasound, Horten, Norway*) with a multi-frequency phased-array transducer. Biplane left ventricular ejection fraction (LVEF) was measured by modified Simpson's rule [20]. Doppler measurements included: mitral inflow early diastole (E) and atrial contraction (A) waves as well as rest and peak stress left ventricular outflow tract (LVOT) pressure gradients obtained from multiple apical views by continuous-wave Doppler [21]. Because LVOT pressure gradients may change with posture, rest and stress pressure gradients were measured under the same position to minimize variation. Study participants underwent transthoracic echocardiogram under left decubitus position before exercise test started, with rest LVOT pressure gradients measured. Once patients completed exercise, they lied back to the examination bed with the same position immediately for peak LVOT pressure gradient measurement. Obstructive HCM was defined as a resting LVOT gradient ≧30 mmHg [9]. Septal early diastolic tissue Doppler (e') velocity was used to calculate E/e' ratio [22].

The outcomes of interest in this study were newly developed hypertension and cardiovascular adverse events. The definition of newly developed hypertension was the same as hypertension at baseline. Cardiovascular adverse events included common complications of HCM, namely new onset atrial fibrillation (AF), new sustained (≥30 s) ventricular tachycardia/fibrillation (VT/VF) with or without appropriate implantable cardioverter defibrillator (ICD) discharge, new onset or worsening of heart failure (HF) [defined as worsening of New York Heart Association (NYHA) functional class to class III or IV] requiring hospitalization, and all-cause mortality [23]. New onset or worsening of HF at NYHA class III or IV had to be documented in outpatient or hospital charts. Arrhythmic outcomes (VT/VF and atrial fibrillation) were recorded by reviewing clinical visit documents, Holter monitoring and ICD interrogation reports. All-cause mortality statistics for the study populations were obtained by linking our database to the Social Security Death Index with a maximal 10-year follow-up. Participants who were enrolled in this study underwent yearly clinic follow-up, stress echocardiography and Holter examination. All events were clinically adjudicated by 1 of 2 HCM clinical experts (T.P.A. and M.R.A.), who also reviewed raw data and electronic documentation of all arrhythmic events. Patients who underwent septal reduction therapy prior to any adverse event were censored 1 day prior to septal reduction therapy.

Descriptive statistics were performed on patient demographics, conventional echocardiographic parameters and exercise hemodynamics stratified by presence or absence of HRE. Data distribution was evaluated with kernel density plots and the Shapiro-Wilk test for normality. Continuous variables were presented as mean ± standard deviation and categorical variables as the total number and percentage. Comparison of variables across groups was performed using Student's t-test for continuous variables and Chi-square test for categorical ones. A binary logistic regression was performed to assess predictors of HRE, and a stepwise linear regression analysis was performed to assess predictors of peak systolic and diastolic blood pressure. Cumulative numbers of adverse CV outcomes were counted at the end of follow-up. Kaplan-Meier analysis of the cardiovascular adverse events was analyzed for the time of enrollment to the first event, with the significance based on the log-rank test. The Cox proportional hazards model was utilized to determine the association of HRE with adverse outcomes. A p-value of <0.05 was considered statistically significant. The analyses were performed using STATA software version 14 (StataCorp LP, College Station, Texas).

3. Results

Six hundred and eighty patients in the HCM registry were initially screened. Three hundred and forty-seven patients had baseline hypertension. The remaining 333 normotensive patients were included in the main analysis **(Supplemental Fig. 1). The mean age** of these 333 participants was 46 ± 14 years, and 67% were men. A hundred and thirty-two (40%) of the 333 participants had HRE. Baseline characteristics are summarized in Table 1. Patients with HRE were more likely to be women, had lower BMI and milder LVOT obstruction. They had similar age and burden of co-morbidities when compared to those without HRE. The use of beta-blockers and calcium channel blockers was also similar.

Patients with or without HRE had similar resting blood pressure, heart rate, exercise time and metabolic equivalents (METs) (Table 1). By definition, patients with HRE had higher peak SBP and DBP, but the peak pulse pressure (PP) was comparable. At peak exercise, patients with HRE had significantly higher maximal heart rate (156 ± 26 vs. 147 ± 29 bpm, p = 0.003), chronotropic response (85 ± 22 vs. 75 ± 23%, p < 0.001), and RPP (25,820 ± 6841 vs. 21,603 ± 7315 bpm*mmHg, p < 0.001). At 1-min post-exercise, patients with HRE displayed greater HR recovery (32 ± 15 vs. 36 ± 14 bpm, p = 0.03). Conversely, patients without HRE were more likely to exhibit ABPR and chronotropic incompetence.

In univariate analysis, women, lower BMI, lower exercise LVOT

Table 1
Baseline characteristics and exercise test results in normotensive HCM patients according to the presence or absence of hypertensive response to exercise (HRE).

	No HRE N = 201	With HRE N = 132	p value
Age, years	45 ± 14	48 ± 15	0.1
Male sex, n (%)	145 (72)	77 (58)	0.01
Body mass index, kg/m^2	29 ± 6	27 ± 5	0.006
Obstructive subtype, n (%)	65 (32)	27 (21)	0.03
Symptoms			
NYHA Fc I, n (%)	124 (62)	88 (67)	0.6
II, n (%)	61 (30)	34 (25)	
III, n (%)	16 (8)	10 (8)	
Angina, n (%)	77 (38)	37 (28)	0.07
Syncope, n (%)	41 (20)	22 (17)	0.5
Co-morbidities			
Atrial fibrillation, n (%)	30 (15)	14 (11)	0.3
Coronary artery disease, n (%)	12 (6)	6 (5)	0.8
Stroke, n (%)	4 (2)	1 (1)	0.7
Diabetes, n (%)	12 (6)	5 (4)	0.5
Echocardiography			
Left atrial diameter, mm	42 ± 8	41 ± 8	0.3
Maximal wall thickness, mm	21 ± 6	21 ± 6	0.9
Septal wall thickness, mm	21 ± 6	21 ± 6	0.9
Posterior wall thickness, mm	12 ± 3	11 ± 3	0.5
Apical hypertrophy, n (%)	26 (13)	15 (11)	0.7
LVEDV, ml	92 ± 30	92 ± 43	0.9
LVESV, ml	32 ± 13	32 ± 15	0.8
LVEF, %	66 ± 8	65 ± 8	0.4
LVSV, ml	60 ± 21	60 ± 34	0.9
E/A ratio	1.6 ± 0.8	1.4 ± 0.6	0.1
E/e' ratio	16.3 ± 8.3	17.6 ± 12.2	0.3
LVOT gradient at rest, mmHg	28 ± 31	23 ± 29	0.08
LVOT gradient at stress, mmHg	71 ± 56	57 ± 49	0.01
Medications			
Beta-blocker, n (%)	131 (65)	74 (56)	0.1
Calcium channel blocker, n (%)	37 (18)	16 (12)	0.2
Disopyramide, n (%)	9 (5)	6 (5)	0.9
Exercise test results			
Bruce protocol, n (%)	174 (87)	115 (87)	0.9
Exercise time, seconds[a]	572 ± 208	608 ± 204	0.1
METs	10.5 ± 4.1	11.4 ± 4.3	0.07
Rest			
SBP, mmHg	126 ± 16	124 ± 17	0.3
DBP, mmHg	76 ± 10	74 ± 12	0.03
MAP, mmHg	93 ± 11	90 ± 13	0.06
PP, mmHg	48 ± 12	49 ± 13	0.4
HR, bpm	66 ± 14	67 ± 14	0.9
Peak exercise			
SBP, mmHg	145 ± 33	165 ± 32	<0.001
DBP, mmHg	70 ± 11	91 ± 15	<0.001
PP, mmHg	77 ± 30	74 ± 31	0.4
MAP, mmHg	95 ± 16	116 ± 16	<0.001
HR, bpm	147 ± 29	156 ± 26	0.003
ABPR, n (%)	95 (47)	30 (23)	<0.001
Achieved target HR, n (%)	84 (15)	91 (13)	<0.001
Peak RPP, bpm[a]mmHg	21603 ± 7315	25820 ± 6841	<0.001
Chronotropic response, %	75 ± 23	85 ± 22	<0.001
Chronotropic incompetence, n (%)	74 (37)	26 (20)	<0.001
HR recovery, bpm	32 ± 15	36 ± 14	0.03

ABPR, abnormal blood pressure response; DBP, diastolic blood pressure; E/A, ratio of early to late diastolic mitral flow velocity; E/e', ratio of early diastolic mitral flow velocity to early diastolic mitral septal annular motion velocity; HCM, hypertrophic cardiomyopathy; HR, heart rate; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; LVSV, left ventricular stroke volume; MAP, mean arterial pressure; NYHA Fc, New York Heart Association functional class; PP, pulse pressure; RPP, rate-pressure product; SBP, systolic blood pressure.

[a] Only included patients on Bruce protocol.

pressure gradients, higher CR and higher HR recovery were associated with HRE, whereas obstructive HCM was inversely associated with the development of HRE. In the multivariate model, CR and women were independently associated with HRE (Table 2).

Peak SBP and DBP were also analyzed as continuous variables.

Table 2
Determinants of hypertensive response to exercise: uni- and multi-variate analysis.

Variable	Uni-variate		Multi-variate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, per year	1.01 (1.00–1.03)	0.1	1.02 (0.99–1.04)	0.07
Women	1.85 (1.16–2.94)	0.009	2.63 (1.49–4.55)	0.001
Body mass index, per kg/m^2	0.94 (0.90–0.99)	0.009	0.97 (0.92–1.02)	0.2
Obstructive subtype	0.54 (0.32–0.90)	0.02	0.65 (0.28–1.49)	0.3
Stress LVOT pressure gradients, per 10 mmHg	0.95 (0.91–0.99)	0.02	0.96 (0.90–1.03)	0.3
Chronotropic response, per 10%	1.24 (1.12–1.38)	<0.001	1.24 (1.08–1.42)	0.002
Heart rate recovery, per 10 bpm	1.21 (1.02–1.43)	0.03	1.06 (0.84–1.33)	0.6

CI, confidence interval; LVOT, left ventricular outflow tract; OR, odds ratio.

Because beta-blocker therapy may attenuate heart rate response during exercise, we stratified our patients according to the use of beta-blockers. Our data showed that CR correlated with both peak SBP and DBP irrespective of the use of beta-blockers (Fig. 1, all $p < 0.05$). In linear regression, sex, BMI, rest SBP, rest DBP, rest LVOT pressure gradients, peak HR, CR and HR recovery correlated with peak SBP (Supplemental Table 1); age, rest SBP, rest DBP, peak HR and CR correlated with peak DBP (Supplemental Table 2). In multivariate analysis, only CR independently correlated with both peak SBP and peak DBP.

In normotensive HCM patients, the presence of HRE was not associated with future development of hypertension. Seventeen patients in the non-HRE group and 11 patients in the HRE group later developed hypertension during follow-up (9 vs. 8%, $p = 0.9$). There were 54 adverse CV events over a mean follow-up of 3.4 ± 2.8 years, including 21 AF, 13 HF, 14 sustained VT/VF and 6 all-cause deaths. Presence of HRE was not associated with higher risk of individual adverse outcome nor the composite outcome (Supplemental Table 3). When the 347 participants with baseline hypertension were also included for comparison, the risks of adverse outcomes across the 3 groups remained comparable (Fig. 2, Supplemental Table 3).

Given that ABPR is one of the major risk factors of sudden cardiac death in HCM [24], a high prevalence of ABPR in patients without HRE may be a confounding factor in risk assessment. When those patients with ABPR were excluded, the comparison of risk trends remained non-significant (progression to hypertension: 7 vs. 9%, $p = 0.7$; adverse CV events: 16 vs. 22%, $p = 0.4$, in patients without or with HRE).

4. Discussion

In this study, we found a high prevalence (40%) of a hypertensive response to exercise among HCM patients. Patients with HRE were more likely to be women, with lower BMI, lower LVOT pressure gradient, better CR and HR recovery. CR and female sex were independently associated with HRE. More importantly, HRE did not carry higher risks of progression to hypertension, major cardiovascular events or all-cause death.

The pathophysiology of HRE has not been clearly understood, and several possible mechanisms have been proposed. Studies have shown that sympathetic nervous system and renin-angiotensin-aldosterone system play a primary role in regulating physiological BP and HR response during exercise [25,26]. Under normal circumstances, endothelium-dependent vasodilation in conduit arteries occurs, as the circulating blood volume and shear stress increase during exercise. Impaired exercise-induced vasodilation and increased peripheral vascular resistance may contribute to HRE [27,28]. It has been reported

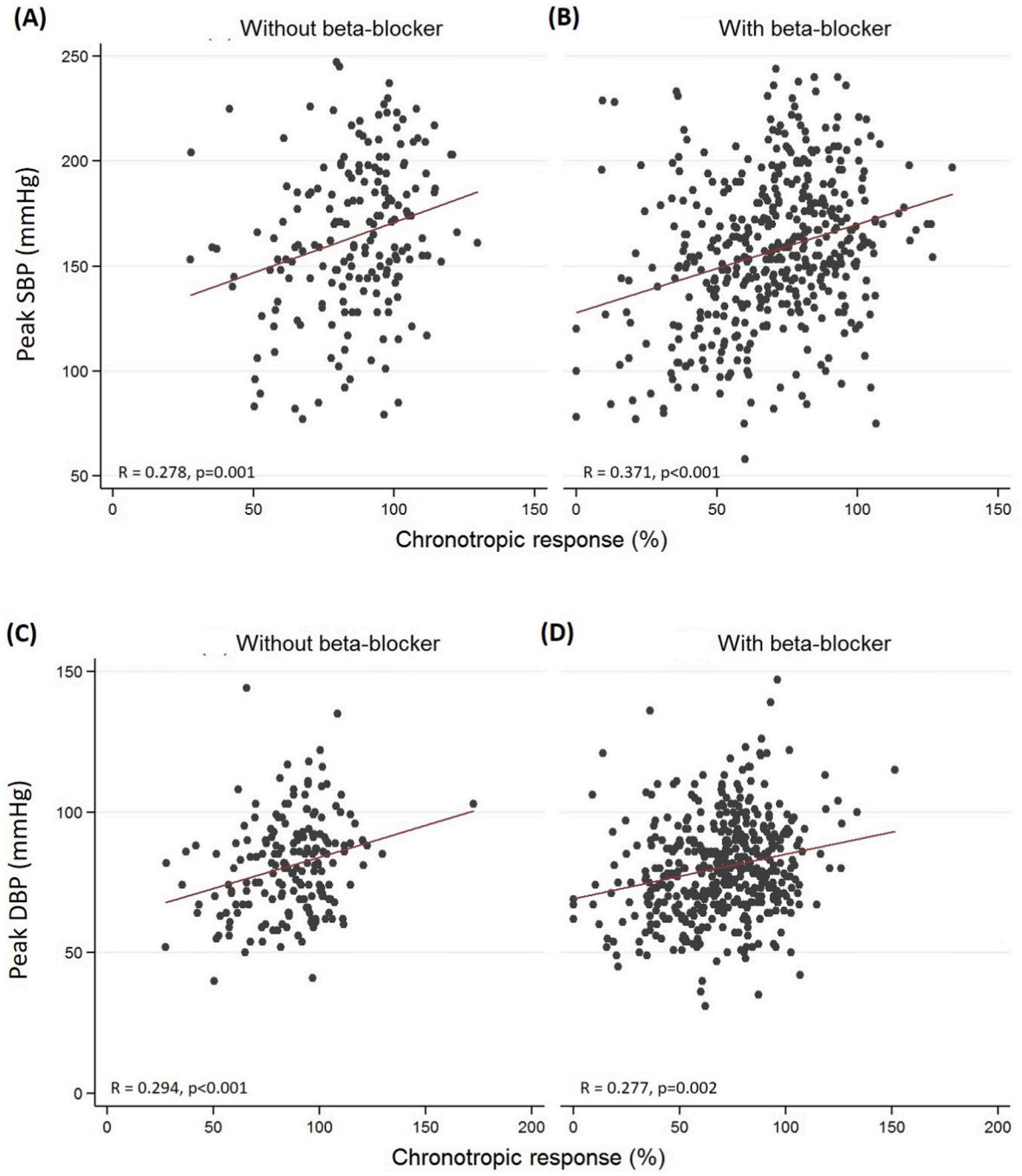

Fig. 1. Regression of peak systolic blood pressure (SBP) during exercise on chronotropic response in patients (A) without beta-blocker or (B) with beta-blocker; and regression of peak diastolic blood pressure (DBP) during exercise on chronotropic response in patients (C) without beta-blocker or (D) with beta-blocker.

that HCM patients demonstrated abnormal aortic stiffness compared to healthy subjects, as indicated by increased pulse wave velocity. Consequently, elevated arterial stiffness reduces arterial compliance and causes excessive BP surge during exercise. This might also explain the high prevalence of HRE among HCM patients.

Dynamic LVOT obstruction, a unique hemodynamic feature in HCM, could also contribute to HRE. The obstruction changes with time and activity. Accordingly, the cardiac output fluctuates in response to varying degrees of obstruction. In our study, the observation that patients with and without HRE had similar rest SBP and PP indicates similar vascular resistance. However, patients with HRE had less LVOT obstruction. A more patent LVOT with minimal obstruction during exercise likely exerts less afterload on the left ventricle, thereby enhancing blood flow into the aorta and consequently resulting in higher forward stroke volume and in turn higher blood pressure.

In a population-based study with 1033 normotensive participants without any use of antihypertensive medications, Miyai et al. found that SBP and DBP were closely associated with HR response during exercise [5]. In the current study, we similarly found a close correlation between exercise BP and increase in heart rate. CR was the only variable that was independently correlated with peak BP and the development of HRE. As cardiac output is determined by stroke volume and heart rate, a higher CR generates higher cardiac output, hence higher peak BP. Taken together, our findings suggest that in normotensive HCM patients, LV stroke volume and HR response might have a stronger impact on the development of HRE than arterial compliance.

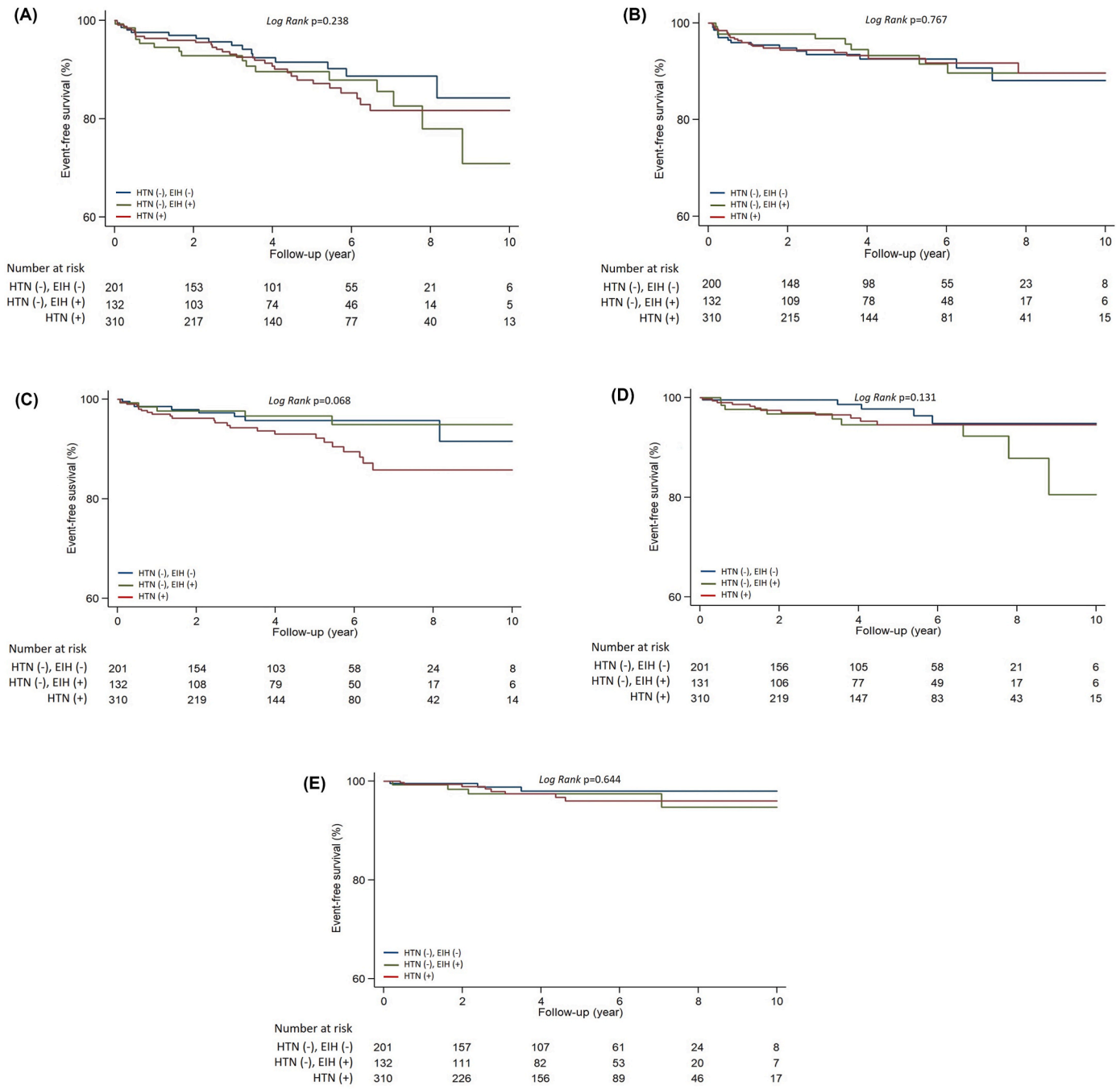

Fig. 2. Kaplan-Meier curves comparing (A) composite outcome, (B) atrial fibrillation (AF), (C) heart failure (HF), (D) ventricular arrhythmia/tachycardia (VTVF) and (E) death in HCM patients.

Thus far, the reported results regarding the prognostic value of HRE have been conflicting. A meta-analysis demonstrated that HRE at moderate exercise intensity during exercise stress test is an independent risk factor for CV events [29]. However, the meta-analysis only enrolled participants who did not have history of myocardial infarction, coronary artery disease or heart failure. It is plausible that among subjects without significant heart conditions, HRE may be more related to the underlying dysregulated vascular resistance than a particular pathological cardiac abnormality. In contrast, other studies reported that higher peak SBP during exercise may indicate better cardiovascular performance. In patients with stable coronary artery disease, increased maximal BP reflected increased maximal myocardial performance [30]. Lauer et al. found that subjects with exercise hypertension had less severe coronary artery disease, better heart rate responses to exercise, and higher RPP indicating greater myocardial oxygen demand [31]. In addition, a higher peak SBP was associated with lower risk of myocardial infarction, heart failure, stroke [7] and overall mortality [8]. In our study, the observation of patients with HRE demonstrating higher CR, higher RPP and better HR recovery might imply that HRE in HCM reflects better cardiac performance. This assumption is somewhat supported by our finding that HCM patients with HRE were not associated with higher risks of future progression to hypertension or adverse CV events. On the other hand, patients without HRE exhibited more severe LVOT obstruction, ABPR and chronotropic incompetence, a marker of advanced disease in HCM patients [32].

Certain limitations need to be considered when interpreting our

results. First, this is a cohort deriving from a single, tertiary referral center. Hence a referral bias might exist. Second, the magnitude of peak HR and BP response to exercise might be underestimated, since 60% of the participants were receiving beta-blockers for the treatment of HCM. As a result, the actual prevalence of HRE in HCM patients could have been higher than what we observed in the present study. Third, HCM patients have been reported to have abnormal aortic stiffness [33]. In the current study, we were not equipped to address how aortic stiffness contributes to the development of HRE in HCM. Therefore, further research focusing on vascular hemodynamics is warranted. Finally, most of our study participants were middle-aged (mean age 46 years) with preserved exercise capacity (10.9 METs in average). Whether the observed benign risk profile of HRE still holds true in elderly HCM subjects needs further investigation.

In conclusions, hypertensive response to exercise is common in HCM patients. CR was independently correlated with peak blood pressure during exercise. More importantly, the presence of HRE was not associated with higher risks of future progression to hypertension or adverse CV events. On the contrary, HCM patients without HRE may warrant monitoring for possible concomitant chronotropic incompetence, severe LVOT obstruction and hypotensive BP response.

Credit author statement

Dai-Yin Lu: Conceptualization, Methodology, Formal analysis, Writing- Original draft preparation. **Ioannis Ventoulis:** Software, Investigation. **Hongyun Liu:** Data Curation Formal analysis. **Bereketeab Haileselassie**: Software. **Iraklis Pozios**: Data Curation. **Hsin-Yueh Liang**: Supervision. **Lars L. Sorensen**: Conceptualization. **Marco Canepa**: Conceptualization. **Nicole Bavaro:** Software. **Susan Phillip**: Software. **M. Roselle Abraham**: Resources Writing- Reviewing and Editing. **Theodore P. Abraham**: Resources Writing- Reviewing and Editing, Project administration, Funding acquisition.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2022.200166.

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