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Exercise Heart Rates in Patients with Hypertrophic Cardiomyopathy

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Abstract

The exercise heart rate (HR) profile and its relationship to cardiac function and arrhythmias was investigated in patients with hypertrophic cardiomyopathy (HC). Chronotropic response (CR) and heart rate recovery (HRR) were computed during and after treadmill exercise testing in 273 HC patients and 95 age-matched healthy controls. HC patients had higher prevalence of chronotropic incompetence and lower HRR_{1–5min} compared to controls. Exercise capacity, diastolic function (assessed by E/e' and left atrial volume index) were associated with HRR_{1min} and CR in HC. Septal myectomy was associated with reduction in chronotropic incompetence, but did not affect HRR_{1min}. In conclusion, impaired CR and HRR_{1min} are associated with advanced disease and do not appear to be independent clinical markers indicating high risk status in HC. Improving CR by titrating doses of negative chronotropic agents, myectomy and atrial pacing may be useful to increase exercise capacity in HC patients.

Keywords

Heart rate recovery; Chronotropic response; Hypertrophic cardiomyopathy

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Introduction

Hypertrophic cardiomyopathy (HC) is the most common genetic cardiovascular disorder, with a prevalence of approximately 1:500 in the general population¹ and the most frequent cause of sudden cardiac death (SCD) in young patients. Hypertrophy, myocyte disarray, electrical remodeling and fibrosis provide a substrate for reentrant arrhythmias, while alterations in autonomic function can serve as triggers for malignant ventricular arrhythmias². In this study, we used the exercise stress test to gather information on the state of the autonomic nervous system and its responsiveness in HC patients. We measured the peak heart rate (HR) response during exercise to assess sympathetic drive to the heart and post-synaptic responsiveness of beta adrenergic receptors in the sino-atrial node³, and post-exercise heart rate recovery (HRR) at 1min to non-invasively quantify parasympathetic function⁴. Blunted chronotropic response (CR) and HRR have been demonstrated to predict mortality in patients with coronary artery disease⁵. However, it is not known whether CR and HRR are markers of risk (mortality, ventricular arrhythmias) in HC. In this study, we assessed CR and HRR (HR profile) during and after a treadmill exercise test and examined the relationship between the HR profile, cardiac function and arrhythmias in 273 patients with a clinical diagnosis of HC.

Methods

This study was approved by the Institutional Review Board at Johns Hopkins. Written informed consent was obtained in all patients. Consecutive, unrelated, adult patients (n=273; 190 men; mean age, 50±15 years) who were seen in the Johns Hopkins HC clinic between 2006 and 2011 were retrospectively studied if they fulfilled the standard diagnostic criteria for HC⁶, namely left ventricular hypertrophy in the absence of other causes such as hypertension and/or valvular disease. Patients were excluded if they were atrially paced, pacemaker dependent or had known pulmonary disease. Mean patient follow up was 37 months. Clinical information, including baseline demographic characteristics, clinical status, cardiac magnetic resonance (CMR), echocardiographic and positron emission tomography (PET) results⁷ were abstracted from the medical record of each subject. The control group consisted of 95 age-matched healthy subjects (56 men; mean age 49±17 years) without evidence of any manifest metabolic or clinical cardiovascular disease.

The clinical information recorded at the initial presentation included: age, gender, symptoms, functional capacity according to the New York Heart Association (NYHA) classification and risk factors for SCD. Based on previous studies, five clinical features were defined as risk factors for SCD in HC: (1) family history of ≥1 HC-related SCD, (2) ≥1 episode of unexplained recent syncope, (3) massive LV hypertrophy (thickness ≥30 mm), (4) non-sustained or sustained ventricular tachycardia (NSVT) on ambulatory 24-hour (Holter monitor) ECG, and (5) hypotensive response to exercise⁸.

ICD discharges and ventricular tachycardia (VT) events were recorded by reviewing Holter and exercise ECG tracings, ICD interrogation reports and clinic visit notes. Sustained VT was considered as ventricular tachycardia with a rate >100 beats per minute and duration >30 seconds or VT that resulted in an ICD discharge. Appropriate ICD discharges were all

confirmed by an electrophysiologist and resulted from ventricular tachyarrhythmias, not arrhythmias such as atrial flutter or fibrillation associated with a rapid ventricular response or device/lead malfunction.

Symptom-limited exercise was performed on a treadmill according to the standard or modified Bruce's protocol. The most common reasons for termination of exercise were dyspnea and fatigue. A physician unaware of the baseline echocardiographic results was present during all studies to encourage maximal exertion. Exercise tolerance was defined by the achieved, estimated metabolic equivalent (METs)⁹.

Peak HR (HR_{peak}) was defined as the HR at the end of the exercise test, while baseline HR ($HR_{baseline}$) was the HR measured with the patient supine, before the exercise test. Heart rate recovery (HRR): HRR was measured as the difference between peak HR and HR at 1–5 min post-exercise, in the supine position with no cool-down period at the end of exercise. Because there are no established criteria for HRR in HC, the lowest quartile in this HC cohort (<20 beats/min [bpm]) was used to define abnormal HRR at 1st min post-exercise, an approach that has been used previously¹⁰.

Chronotropic response (CR): CR was assessed by calculating the percentage of HR reserve used: $(peak\ HR - baseline\ HR) / (220 - age - baseline\ HR) \times 100\%$ ^{11,12}. Chronotropic incompetence (CI): CI was defined as a low proportion of HR reserve used: a cut-off value of $<80\%$ ^{5,11,13} was used in patients not receiving beta blockers, and $<62\%$ in patients receiving beta blocker therapy¹⁴.

A normal BP response was defined as an increase of at least 20 mmHg in systolic BP during exercise, with a gradual decline during recovery¹⁵. Impaired BP responses were defined as either (1) an initial increase in systolic BP with a subsequent fall of >20 mmHg compared with the BP value at peak exercise or a continuous decrease in systolic BP throughout the exercise test of >20 mmHg compared with resting BP (termed hypotensive responses) or (2) an increase of <20 mmHg in systolic BP from resting state to peak exercise (termed a flat response).

A standard clinical scanning protocol was implemented in all subjects using a GE Vivid 7 ultrasound machine (GE Ultrasound, Milwaukee, WI) equipped with a multi-frequency phased-array transducer. Complete 2-dimensional and Doppler echocardiograms were analyzed offline by a single observer who was blinded to patient factors. All echocardiographic parameters were averaged over 3 cardiac cycles or 3 measurements. Peak left ventricular outflow tract gradients were measured at rest and following exercise in all HC patients.

A subset ($n=205$) of HC patients underwent CMR before and after administration of 0.2 mmol/kg of Gadopentate Dimeglumine (Magnevist, Shering), using a 1.5-T clinical scanner (Siemens Avanto, Erlangen, Germany) and a phased-array receiver coil placed on the chest. A semi-automated threshold technique using 6 standard deviations above the mean signal intensity of the normal nulled myocardium was used to assess delayed enhancement (DE)¹⁶.

A subset (n=51) of HC patients underwent perfusion PET imaging using $^{13}\text{-NH}_3$ to assess for inducible ischemia. PET was performed using a GE Discovery VCT PET/CT system. Coronary vasodilation was achieved by administration of Dipyridamole (0.56 mg/kg) or Regadenoson (0.4 mg). For myocardial blood flow quantification, volumetric sampling of the myocardial tracer activity was performed by manual definition of the long heart axis, followed by software computation and displayed as a static polar map. Subsequently, the static polar map-defined segments were reapplied to dynamic imaging series in order to create quantitative polar maps, and thus, myocardial time–activity curves (TAC). A small region of interest was positioned in the LV cavity to obtain the arterial input function. Utilizing these data, myocardial blood flow (MBF) was calculated by fitting the arterial input function and myocardial TAC from the dynamic polar maps to a well-established 2 tissue-compartment tracer kinetic model. This model includes corrections for potential underestimation of tissue activity due to partial volume effect and spillover activity from the left and right ventricular cavities into the myocardial wall. Global left ventricular MBF during vasodilator-stress and rest was measured in milliliters/minute/gram (ml/min/gm).

Quantitative variables are expressed as central tendency and dispersion measures, opting for mean and standard deviation or median and interquartile deviation (based on dispersion of data). Categorical variables are presented as relative frequencies. Student's t-test and ANOVA were used as parametric tests. The fulfillment of normality assumption was evaluated using the Shapiro-Wilk test and homogeneity of variance. Non-parametric tests (Mann–Whitney U and Kruskal-Wallis tests) were used if the assumptions of normality were not met. In order to establish association between categorical variables, chi-square test was used; when Cochran's rule was not met, Fisher's exact test was used. Correlation between quantitative variables was assessed using the Pearson correlation coefficient. The Bonferroni correction was used in the case of multiple tests. A linear regression model was used to analyze factors that affect $\text{HRR}_{1\text{min}}$ and CR. Residual analysis and identification of influential points was performed to establish the best model. A p-value <0.05 was considered statistically significant.

HRR was defined as abnormal based on the lowest quartile of HR during the 1st min of recovery in our study population, an approach that has been used before (20 beats/min [bpm])¹⁰. All statistical analysis was performed using SPSS Statistical software.

Results

Consecutive HC patients were studied. The control group consisted of 95 age-matched healthy subjects. All HC patients and controls were in sinus rhythm. HC patients had a higher prevalence of chronotropic incompetence (CI) ($p<0.001$) and lower HRR indices at 1–5min post-exercise (Table 1). $\text{HRR}_{1\text{min}}$ was positively correlated with peak heart rate during exercise (Figure 1) in HC patients. An abnormal BP response to exercise was seen in 10% of the HC patients and 7% of the controls.

HC patients were classified into two groups (normal and blunted HRR) based on HRR at 1min (Table 2). HC patients who exhibited a blunted HRR at 1min post-exercise, presumably due to impaired vagal reactivation, had a higher proportion of NYHA class

III/IV symptoms, angina, lower peak exercise capacity and heart rates, higher LV mass, higher rest LVOTG (left ventricular outflow tract gradients), worse diastolic function (larger left atrium, higher E/e') and higher prevalence of DE by CMR, than HC patients with normal HRR (Table 2), suggesting advanced disease.

Chronotropic incompetence (CI) was seen in 31% of HC patients. Patients with CI had lower HR at baseline, were older, with higher prevalence of NYHA class III/IV symptoms, and demonstrated lower exercise capacity, delayed HRR_{1min} post-exercise, higher rest LVOT gradients and greater diastolic dysfunction (reflected by higher E/e') than HC patients who had a normal CR to exercise (Table 2). However, there was no difference in left atrial (LA) volumes, prevalence of DE by CMR, and stress/rest MBF between the 2 groups.

HC patients with normal HRR_{1min} and CR were younger, had the highest exercise capacity, lowest rest LVOT gradients and better diastolic function (manifested by lowest LA volume/index and E/e'), when compared to the rest of the HC cohort (Table 3). Impairment of CR and HRR_{1min} was seen in 20% of HC patients—this sub-group had the highest prevalence of DE on CMR, when compared to the rest of the HC cohort. Isolated impairment of HRR_{1min} or CR was seen in 4% and 31% patients respectively (Table 3).

A trend towards higher frequency of ventricular arrhythmias, manifested by higher number of ICD discharges for ventricular tachycardia/fibrillation (VT/VF), greater prevalence of non-sustained VT and history of sustained VT/VF was observed in patients with abnormal CR only, but not in patients with abnormal CR + HRR_{1min} (Table 4). Patients with normal CR and HRR_{1min} had fewer risk factors for SCD than the remainder of the subgroups (Table 4).

Beta blockers are the first line of therapy in patients with obstructive and non-obstructive HC. Patients presenting with obstructive HC often receive high doses of beta blockers, with the aim of reducing LVOT obstruction. In this study, 62% of HC patients were receiving beta blocker therapy at the time of their first stress test. Beta blocker use was associated with faster HRR at 3–5min post-exercise in HC patients with normal HRR_{1min} ; trends did not reach statistical significance in patients with abnormal HRR_{1min} , which could reflect decreased autonomic responsiveness in this subgroup.

A subset of HC patients (n=39) underwent surgical septal myectomy for relief of left ventricular outflow tract obstruction. Myectomy was associated with a reduction in chronotropic incompetence, but did not affect HRR_{1min} . The prevalence of abnormal BP response to exercise was also reduced by myectomy, possibly by increasing cardiac output during exercise and/or preventing reflex activation of exaggerated peripheral vasodilation.

In multivariate analysis, exercise capacity (METs) and LA volume index had the strongest independent association with HRR_{1min} and CR. Of all the imaging parameters examined, E/e' had the best linear correlation with HRR_{1min} and CR (Figure 2A, B).

Discussion

This study reveals that impairment of CR and HRR_{1min} are frequent in HC and highlights the importance of assessing chronotropic response in HC patients. Chronotropic incompetence and impaired HRR are associated with advanced disease and do not appear to be unique, independent markers of high risk status in HC.

Exercise capacity (METs) was strongly associated with CR and HRR_{1min}. Since 62% of HC patients were receiving beta blockers, beta blocker use is probably an important contributor to chronotropic incompetence, especially in patients with obstructive HC, who are prescribed high doses of beta blockers, calcium channel blockers and/or disopyramide. Chronotropic incompetence in HC could also reflect damage to cardiac sympathetic nerve fibers/neurons, advanced disease with reduced beta adrenoreceptor density/sensitivity, electrophysiological remodeling and/or fibrosis in the region of the sino-atrial node¹⁷ with resultant impaired sympathetic responsiveness. A trend towards increased risk for ventricular arrhythmias was seen in HC patients with impaired CR, suggesting that it could be a marker for pro-arrhythmic electrophysiologic remodeling in the left ventricle in HC.

Isolated impairment of HRR_{1min} was seen in only 4% of the HC population whereas ~20% of HCM patients had both CI and delayed HRR at early (1~2min) and late time points (>2 min post-exercise), suggesting blunted parasympathetic signaling and possibly, augmented sympathetic signaling to the heart. Possible mechanisms underlying these results are impaired baroreceptor sensitivity resulting in increased sympathetic outflow, combined with reduced beta adrenoreceptor density and/or sensitivity¹⁸ and reduced catecholamine reuptake by myocardial sympathetic nerve terminals¹⁹. Interestingly, beta blockers did not affect HRR (at later time points) in patients with impaired HRR_{1min}, the majority (81%) of whom had concomitant chronotropic incompetence, suggesting that these patients could have structural changes in the SA node resulting in impaired autonomic responsiveness. In support of this hypothesis, patients with impaired HRR had a high prevalence of DE by CMR (Table 3).

Prognostic implications of abnormal CR and HRR_{1min} have been examined in large numbers of patients with coronary artery disease²⁰. Based on these results, we expected that patients with impairment of CR + HRR would be most susceptible to ventricular arrhythmias, but were surprised to find that patients with chronotropic incompetence only, had a trend for higher incidence of ventricular arrhythmias. (Table 4). We observed a linear relationship between CR and HRR_{1min} in HC patients (Figure 1), which could also explain the low prevalence of isolated impairment of HRR_{1min} (4%) in the HC population. Given the relationship between peak HR and HRR, impaired HRR_{1min} in HC patients with chronotropic incompetence may not always reflect reduced vagal reactivation. This could provide an explanation for our finding of low incidence of ventricular arrhythmias in patients with impaired CR + HRR_{1min}, compared to patients with impaired CR alone (Table 4).

We found correlations between diastolic function evaluated by E/e', which reflects left ventricular end-diastolic pressure, with HRR_{1min} and CR, suggesting that an abnormal heart

rate profile during exercise in most likely secondary to advanced disease. The mechanism underlying the link between diastolic function and heart rate profile is not known, but could include increased myocardial Angiotensin II levels and activation of oxidized CAMKII-mediated signaling, resulting in alteration of sino-atrial/ventricular myocyte electrophysiology and fibrosis²¹. The association between exercise capacity and CR highlights the importance of assessing CR in HC patients presenting with exercise intolerance. Our study suggests that septal myectomy, titration of doses of negatively chronotropic agents such as beta blockers, calcium channel blockers, disopyramide and atrial pacing may be useful to improve exercise capacity in HC patients.

This is an observational, retrospective single center study that did not investigate the effects of beta blocker dose or parasympathetic blockade on CR or HRR_{1min}. Plasma catecholamine levels which would have enabled confirmation of globally increased sympathetic activity were not measured. However, previous studies indicated that global indices of sympathetic function provide little information on the regional patterning of sympathetic nervous responses²² and that quantification of regional sympathetic nerve outflow is needed. Relatively short follow up precludes assessment of whether myopathy leads to autonomic dysfunction in HC. Lastly, no measurements of habitual physical activity or body composition (which could affect HR responses during and after exercise) were performed in the HC patients or controls.

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Figure 1.

Linear regression between HRR_{1min} and peak heart rate during exercise: HRR_{1min} is positively correlated with peak heart rate.

HRR_{1min} : Heart rate at 1 minute post exercise.; Peak HR: Peak heart rate.

Figure 2.

A, B. E/e' had the best linear correlation with HRR_{1min} and chronotropic response.

HRR_{1min}: Heart rate recovery at 1 minute post exercise.

Table 1

Heart rate recovery, chronotropic response and blood pressure response to exercise in hypertrophic cardiomyopathy patients and controls

Variables	HC (n=273)	Controls (n=95)	p-value
HRR _{1min} (bpm)	29±9	34±6	0.004 *
HRR _{2min} (bpm)	46±12	58±7	<0.0001 *
HRR _{3min} (bpm)	54±13	70±8	<0.0001 *
HRR _{4min} (bpm)	58±13	76±8	<0.0001 *
HRR _{5min} (bpm)	59±12	80±8	<0.0001 *
Percentage of CI	0.52	0.15	<0.001 ⁺
Percentage with ABPR	0.097	0.07	<0.001

HC: hypertrophic cardiomyopathy; HRR.: heart rate recovery; bpm: beats per minute; CI: chronotropic incompetence; ABPR: abnormal blood pressure response.

HRR=Peak HR-HR at 1–5minutes post-exercise.

* U Mann Whitney Test

⁺ Chi2 test

Clinical and imaging characteristics of hypertrophic cardiomyopathy patients with normal or reduced heart rate recovery_{1min}, normal chronotropic response and chronotropic incompetence

Table 2

Variables	HRR _{1min} >20 bpm (n=203)	HRR _{1min} 20 bpm (n=70)	p-value	Chronotropic incompetence (n=142)	Normal CR (n=131)	p-value
Clinical Variables						
Age (yrs)	49±9	58±8	<0.0001*	52±13	47±16	0.0041**
Gender (male)	0.72	0.61	0.08 ⁺	0.68	0.71	0.63 ⁺
NYHA class (3, 4)	0.04	0.23	<0.001 ⁺	0.14	0.05	<0.001 ⁺
Angina	0.2	0.36	0.006 ⁺	0.31	0.18	0.019 ⁺
Dyspnea	0.4	0.72	<0.001 ⁺	0.63	0.34	<0.001 ⁺
Beta-blockers	0.6	0.63	0.6 ⁺	0.73	0.58	<0.001 ⁺
ABPR	0.24	0.58	0.1 ⁺	0.33	0.2	0.014 ⁺
Baseline HR (bpm)	73±8	72±10	0.6*	68±7.5	78±8	<0.0001*
Peak HR (bpm)	154±25	120±26	<0.001**	130±13.5	170±13	<0.0001*
Total Exercise Time (s)	596±189	380±218	<0.001	480±204	622±202	<0.001
METs	11.3±2.5	6.85±1.6	<0.0001*	8.3±2	12.85±2.9	<0.0001*
HRR Variables						
HRR _{1min} (bpm)	-	-	-	25±8.5	35±8	<0.0001*
HRR _{2min} (bpm)	50±8	26±5	<0.0001*	37±10.5	54±8.5	<0.0001*
HRR _{3min} (bpm)	59±19	33±7	<0.0001*	42±16	64±15	<0.0001**
HRR _{4min} (bpm)	63±15	36±13	<0.0001**	46±16	69±15	<0.0001**
HRR _{5min} (bpm)	66±10	38±8	<0.0001*	46±10.8	70±16.8	<0.0001*
Imaging Variables						
Maximal IVS (cm)	2±0.3	2.1±0.3	0.3*	2±0.35	2±0.35	0.6608*
LV Mass (g)	241±52	267±56	0.02*	254±52.5	235±54	0.0398*
LVOT peak gradient-rest (mm Hg)	12±10	21±17	0.003*	19.5±18	10±7.5	0.0001*
LVOT peak gradient-stress (mm Hg)	43±39	54±39	0.305*	56.5±37	36±26.5	0.0557*

Variables	HRR _{1min} >20 bpm (n=203)	HRR _{1min} 20 bpm (n=70)	p-value	Chronotropic incompetence (n=142)	Normal CR (n=131)	p-value
LA Volume (ml)	68±19	88±27	0.003 [*]	75±22	62±20	0.0089 [*]
LAVI (ml/m ²)	34±8.5	39±9	0.019 [*]	36±8.5	32±8	0.0161 [*]
LVEF (%)	68±7	69±5	0.5 [*]	70±6.5	67±7	0.0083 [*]
MV E/A	1.2±0.2	1.1±0.3	0.02 [*]	1.2±0.3	1.2±0.26	0.6226 [*]
MV E/e'	15±4	18.5±6	0.003 [*]	18±5.5	14±3.5	<0.0001 [*]
Patients with DE on CMR (%)	64	78	0.09 [†]	71	64	0.303 [†]
Stress MBF (ml/min/gm)	2.0±1.1	2.1±0.8	0.7	2.0±0.8	2.1±0.9	0.8
Rest MBF (ml/min/gm)	0.9±0.2	0.9±0.3	0.7	0.9±0.3	0.9±0.3	0.8

ABPR: abnormal blood pressure response to exercise; CMR: cardiac magnetic resonance; CR: chronotropic response; DE: delayed enhancement; HRR: heart rate; HRR: heart rate recovery; IVS: inter-ventricular septum; LA: left atrium; LAVI: left atrial volume index; LV: left ventricle; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; MBF: myocardial blood flow; METs: metabolic equivalents; MV: mitral valve; NYHA: New York Heart Association.

^{*} U Mann Whitney Test

^{**} T Student Test

[†] Chi2 Test

Clinical and imaging characteristics of hypertrophic cardiomyopathy subgroups with normal heart rate recovery and chronotropic response, abnormal chronotropic response only, abnormal heart rate recovery only, abnormal heart rate recovery and chronotropic response

Table 3

Variables	Normal HRR _{1min} and CR (n=118)	Abnormal CR (n=85)	Abnormal HRR _{1min} (n=13)	Abnormal HRR _{1min} and CR (n=57)	p-value
Clinical Variables					
Age (yrs)	46±15	49±12	61±14	57±12	<0.0001 [*]
Gender (male)	0.73	0.72	0.54	0.63	0.3 ⁺
NYHA (3,4)	0.03	0.05	0.15	0.19	0.001
Angina	0.18	0.24	0.23	0.4	0.01 ⁺
Dyspnea	0.31	0.54	0.62	0.75	<0.0001 ⁺
Beta-blockers	0.47	0.78	0.54	0.65	<0.0001 ⁺
Percentage ABPR	0.21	0.29	0.08	0.4	0.02 ⁺
Baseline HR (bpm)	78±13	68±12	93±16	71±13	<0.0001 [*]
Peak HR (bpm)	170±17	134±16	156±14	114±21	<0.001
Exercise Time (s)	649±189	529±171	379±154	406±227	<0.001
METs	13±3	9.7±2	7.2±1.7	6.6±1.5	0.0001 ^{**}
HRR (bpm)					
HRR _{2min}	56±8	44±6	33±3	24±5	0.0001 ^{**}
HRR _{3min}	65±8	49±8	43±5	31±7	0.0001 ^{**}
HRR _{4min}	68±8	54±7	48±10	34±6	0.0001 ^{**}
HRR _{5min}	70±7	54±9	50±7	35±7	<0.0001 ^{**}
Imaging Variables					
Maximal IVS (cm)	2.0±0.5	2.1±0.5	2.3±0.7	2.1±0.5	0.6 [*]
LV Mass (g)	233±50	250±50	312±83	266±44	0.04 ^{**}
LVOT peak Gradient-rest (mm Hg)	10±6	17±18	12.5±16	22±17	0.0003 ^{**}
LVOT peak Gradient-stress (mm Hg)	36±25	53±36	32±50	62±37	0.2 ^{**}
LA Volume (ml)	62±20	70±18	80±65	83±18	0.006 ^{**}
LAVI (ml/m ²)	30±8	35±8	40±31	39±9	0.02 ^{**}

Variables	Normal HRR _{1min} and CR (n=118)	Abnormal CR (n=85)	Abnormal HRR _{1min} (n=13)	Abnormal HRR _{1min} and CR (n=57)	p-value
LVEF (%)	66±11	697±10	65±9.54	69±10	0.06 [*]
MV E/A	1.2±0.2	1.2±0.2	0.99±0.2	1.1±0.3	0.1 ^{**}
MV E/e'	14±3.5	18±5	17±4.5	19±7	0.0001 ^{***}
Patients with DE on CMR (%)					
	0.606	0.535	0.666	0.812	0.04 [†]
Stress MBF (ml/min/gm)	2.0±0.9	2.2±0.8	2.0±0.3	1.8±0.3	0.5
Rest MBF (ml/min/gm)	0.9±0.3	0.9±0.3	0.8±0.5	0.8±0.3	0.7

ABPR: abnormal blood pressure response to exercise; BP: blood pressure; CR: chronotropic response; DBP: diastolic blood pressure; DE: delayed enhancement; HR: heart rate; HRR: heart rate recovery; IVS: inter-ventricular septum; LA: left atrium; LAVI: left atrial volume index; LV: left ventricle; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; MBF: myocardial blood flow; METs: metabolic equivalents; MV: mitral valve; NYHA: New York Heart Association; SBP: systolic blood pressure.

^{*} Oneway ANOVA

^{**} Kruskal Wallis Test

[†] Chi squared test

Clinical outcomes of hypertrophic cardiomyopathy subgroups based on heart rate recovery and chronotropic response

Table 4

Variables	Normal HRR _{min} and CR (n=118)	Abnormal CR only (n=85)	Abnormal HRR _{min} only (n=13)	Abnormal HRR _{min} and CR (n=57)	p-value
ICD (%)	21	39	19	28	0.06
Arrhythmias ICD discharge for VT/VF (%)	1.8	4.9	0	0	0.3*
NSVT (%)	6.7	11.3	10	0	0.07*
History of sustained VT/VF (%)	0.9	2.4	0	0	0.6*
Death (%)	0	1.4	0	2.1	0.3*
Cumulative number of risk factors for SCD					
0 risk factor (%)	45	32	30	17	0.02
1 risk factor (%)	34	45	70	38	0.12
2 risk factors (%)	22	28	30	41	0.05

CR: Chronotropic Response; HRR: Heart Rate Recovery; ICD: implantable cardioverter defibrillator; NSVT: Non-sustained ventricular tachycardia; SCD: sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

* Fisher's exact test