Exercise Heart Rates in Patients With Hypertrophic Cardiomyopathy

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The exercise heart rate (HR) profile and its relation to cardiac function and arrhythmias were 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 patients with HC and 95 age-matched healthy controls. Patients with HC had higher prevalence of chronotropic incompetence and lower HRR_{1-5min} compared with 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 patients with HC. © 2015 Elsevier Inc. All rights reserved. **(Am J Cardiol 2015;115:1144−1150)**

Hypertrophic cardiomyopathy (HC) is the most common genetic cardiovascular disorder, with a prevalence of approximately 1:500 in the general population[1] 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, whereas alterations in autonomic function can serve as triggers for malignant ventricular arrhythmias.[2] In this study, we used the exercise stress test to gather information on the state of the autonomic nervous system and its responsiveness in patients with HC. We measured the peak heart rate (HR) response during exercise to assess sympathetic drive to the heart and postsynaptic responsiveness of β-adrenergic receptors in the sinoatrial node[3] and post-exercise heart rate recovery (HRR) at 1 minute to non-invasively quantify parasympathetic function.[4] Blunted chronotropic response (CR) and HRR have been demonstrated to predict mortality in patients with coronary artery disease.[5] However, it is not known whether CR and HRR are markers of risk (mortality and ventricular arrhythmias) in HC. In this study, we assessed CR and HRR (HR profile) during and after a treadmill exercise test and examined the relation 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 from 2006 to 2011 were retrospectively studied if they fulfilled the standard diagnostic criteria for HC,[6] 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, and cardiac magnetic resonance (CMR), echocardiographic, and positron emission tomography (PET) results[7] 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, 5 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) nonsustained or

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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

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

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

* U Mann Whitney Test.

† Chi-square test.

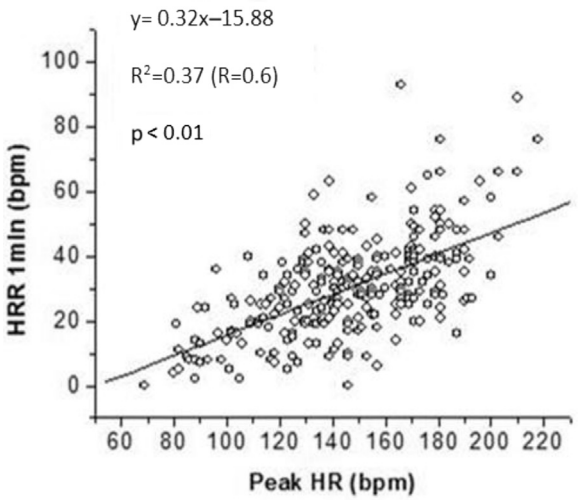

Figure 1. Linear regression between HRR_{1min} and peak HR during exercise: HRR_{1min} is positively correlated with peak HR. HRR_{1min} = heart rate at 1 minute after exercise.

sustained ventricular tachycardia (VT) on ambulatory 24-hour (Holter monitor) electrocardiography, and (5) hypotensive response to exercise.[8]

Implantable cardioverter defibrillator (ICD) discharges and VT events were recorded by reviewing Holter and exercise electrocardiographic tracings, ICD interrogation reports, and clinic visit notes. Sustained VT was considered as VT with a rate >100 beats/min 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 (MET).[9]

Peak HR (HR_{peak}) was defined as the HR at the end of the exercise test, whereas baseline HR ($HR_{baseline}$) was the HR measured with the patient supine before the exercise test. HRR was measured as the difference between peak HR and HR at 1 to 5 minutes after 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) was used to define abnormal HRR at first minute after exercise, an approach that has been used previously.[10]

Chronotropic response (CR) was assessed by calculating the percentage of HR reserve used: (peak HR − baseline HR)/(220 − age − baseline HR) × 100%.[11,12] Chronotropic incompetence (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 β blockers and <62% in patients receiving β-blocker therapy.[14]

A normal BP response was defined as an increase of at least 20 mm Hg in systolic BP during exercise, with a gradual decrease during recovery.[15] Impaired BP responses were defined as either (1) an initial increase in systolic BP with a subsequent decrease of >20 mm Hg compared with the BP value at peak exercise or a continuous decrease in systolic BP throughout the exercise test of >20 mm Hg compared with BP at rest (termed hypotensive responses) or (2) an increase of <20 mm Hg 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, Wisconsin) equipped with a multifrequency 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 after exercise in all patients with HC.

A subset (n = 205) of patients with HC underwent CMR before and after administration of 0.2 mmol/kg of Gadopentate Dimeglumine (Magnevist; Shering, Germany), 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 SDs more than the mean signal intensity of the normal nulled myocardium was used to assess delayed enhancement (DE).[16]

A subset (n = 51) of patients with HC underwent perfusion PET imaging using 13-NH3 to assess for inducible ischemia. PET was performed using a GE Discovery VCT PET/CT System (Waukesha, Wisconsin). Coronary vasodilation was achieved by administration of *Dipyridamole* (0.56 mg/kg) or *Regadenoson* (0.4 mg). For myocardial blood flow (MBF) 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 to create quantitative polar maps and, thus, myocardial time-activity curves. A small region of interest was positioned in the LV cavity to obtain the arterial input function. Using these data, MBF was calculated by fitting the arterial input function and myocardial time-activity curves from the dynamic polar

Table 2
Clinical and imaging characteristics of hypertrophic cardiomyopathy patients with normal or reduced heart rate recovery$_{1min}$, normal chronotropic response and chronotropic incompetence

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 (mmHg)	43±39	54±39	0.305*	56.5±37	36±26.5	0.0557*
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; 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.

* U Mann Whitney Test.

† T Student Test.

‡ Chi-square Test.

maps to a well-established 2-tissue compartment tracer kinetic model. This model includes corrections for potential underestimation of tissue activity because of 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 per minute per gram (ml/min/g).

Quantitative variables are expressed as central tendency and dispersion measures, opting for mean and SD or median and interquartile deviation (based on dispersion of data). Categorical variables are presented as relative frequencies. Student's *t* test and analysis of variance were used as parametric tests. The fulfillment of normality assumption was evaluated using the Shapiro-Wilk test and homogeneity of variance. Nonparametric tests (Mann-Whitney *U* and Kruskal-Wallis tests) were used if the assumptions of normality were not met. 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 HRR_{1min} and CR. Residual analysis and identification of influential points were 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 first minute of recovery in our study population, an approach that has been used before (≤20 beats/min).[10] Statistical analysis was carried out using the computer software Statistical Program for Social Sciences (SPSS) 17.0 (Chicago, Illinos).

Table 3
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

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†
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 = interventricular 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.

Results

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

Patients with HC were classified into 2 groups (normal and blunted HRR) based on HRR at 1 minute (Table 2). Patients with HC who exhibited a blunted HRR at 1 minute after exercise, presumably because of impaired vagal reactivation, had a higher proportion of NYHA class III/IV symptoms, angina, lower peak exercise capacity and HRs, higher LV mass, higher rest left ventricular outflow tract gradients (LVOTGs), worse diastolic function (larger left atrium, higher E/e'), and higher prevalence of DE by CMR than patients with HC with normal HRR (Table 2), suggesting advanced disease.

CI was seen in 31% of patients with HC. 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} after exercise, higher rest LVOTGs, and greater diastolic dysfunction (reflected by higher E/e') than patients with HC 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.

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

Table 4
Clinical outcomes of hypertrophic cardiomyopathy subgroups based on heart rate recovery and chronotropic response

Variables	Normal HRR_{1min} and CR (n=118)	Abnormal CR only (n=85)	Abnormal HRR_{1min} only (n=13)	Abnormal HRR_{1min} 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.

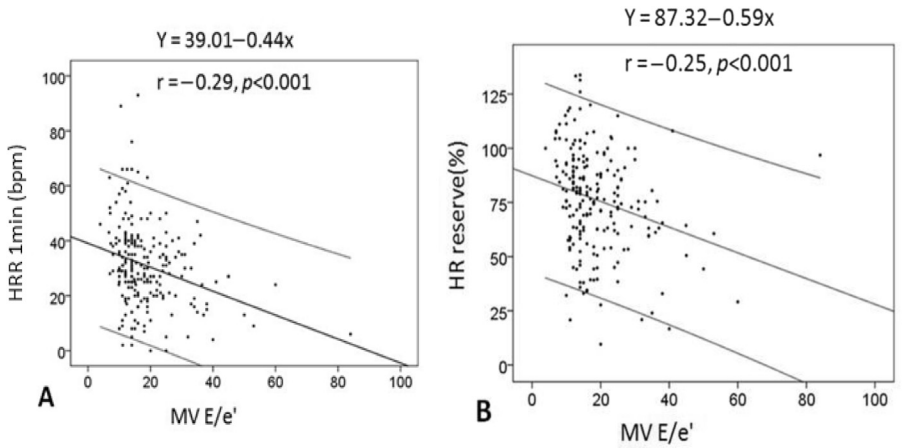

Figure 2. *(A and B)*: E/e' had the best linear correlation with HRR_{1min} and chronotropic response. HRR_{1min}: HR recovery at 1 minute after exercise.

CR was seen in 4% and 31% patients, respectively (Table 3).

A trend toward higher frequency of ventricular arrhythmias, manifested by higher number of ICD discharges for ventricular tachycardia/fibrillation (VT/VF), greater prevalence of nonsustained 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 nonobstructive HC. Patients presenting with obstructive HC often receive high doses of β blockers, with the aim of reducing LVOT obstruction. In this study, 62% of patients with HC were receiving β-blocker therapy at the time of their first stress test. Beta-blocker use was associated with faster HRR at 3 to 5 minutes after exercise in patients with HC 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 patients with HC (n = 39) underwent surgical septal myectomy for relief of left ventricular outflow tract obstruction. Myectomy was associated with a reduction in CI 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 2).

Discussion

This study reveals that impairment of CR and HRR_{1min} are frequent in HC and highlights the importance of assessing CR in patients with HC. CI 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}. Because 62% of patients with HC were receiving β blockers, β-blocker use is probably an important contributor to CI, especially in patients with obstructive HC, who are prescribed high doses of β blockers, calcium channel blockers, and/or disopyramide. CI in HC could also

reflect damage to cardiac sympathetic nerve fibers/neurons, advanced disease with reduced β-adrenoreceptor density/sensitivity, electrophysiological remodeling, and/or fibrosis in the region of the sinoatrial node[17] with resultant impaired sympathetic responsiveness. A trend toward increased risk for ventricular arrhythmias was seen in patients with HC with impaired CR, suggesting that it could be a marker for pro-arrhythmic electrophysiological 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 to 2 minutes) and late time points (>2 minutes after 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 β-adrenoreceptor density and/or sensitivity,[18] and reduced catecholamine reuptake by myocardial sympathetic nerve terminals.[19] Interestingly, β blockers did not affect HRR (at later time points) in patients with impaired HRR_{1min}, the majority (81%) of whom had concomitant CI, suggesting that these patients could have structural changes in the sinoatrial 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 disease.[20] 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 CI only had a trend for higher incidence of ventricular arrhythmias (Table 4). We observed a linear relation between CR and HRR_{1min} in patients with HC (Figure 1), which could also explain the low prevalence of isolated impairment of HRR_{1min} (4%) in the HC population. Given the relation between peak HR and HRR, impaired HRR_{1min} in patients with HC with CI 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 with 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 HR profile during exercise is most likely secondary to advanced disease. The mechanism underlying the link between diastolic function and HR profile is not known but could include increased myocardial angiotensin II levels and activation of oxidized Ca^{2+}-calmodulin-dependent protein kinase II (CAMKII)-mediated signaling, resulting in alteration of sinoatrial/ventricular myocyte electrophysiology and fibrosis.[21] The association between exercise capacity and CR highlights the importance of assessing CR in patients with HC presenting with exercise intolerance. Our study suggests that septal myectomy, titration of doses of negatively chronotropic agents such as β blockers, calcium channel blockers, disopyramide, and atrial pacing may be useful to improve exercise capacity in patients with HC.

This is an observational, retrospective single-center study that did not investigate the effects of β-blocker dose or parasympathetic blockade on CR or HRR_{1min}. Plasma catecholamine levels that 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 responses[22] 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 patients with HC or controls.

Disclosures

The authors have no conflicts of interest to disclose.

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