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Exercise hemodynamics in hypertrophic cardiomyopathy identify risk of incident heart failure but not ventricular arrhythmias or sudden cardiac death☆

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ABSTRACT

Objective: To determine whether abnormal blood pressure response (ABPR), with or without left ventricular outflow tract obstruction (LVOTO), is associated with adverse heart failure and arrhythmia outcomes in hypertrophic cardiomyopathy (HCM).
Methods: A retrospective, single-center analysis was performed for adult HCM patients who underwent exercise stress testing.
Results: Of 589 patients included in the study, 192 (33%) demonstrated ABPR. A similar proportion of patients with ABPR had LVOTO compared to those without ABPR (56% vs 63%, $p = 0.11$). Patients with ABPR demonstrated lower percent predicted VO2 and METs achieved than those with LVOTO (16.9 ± 6.8 vs 21.6 ± 7.9, $p = 0.002$ and 5.3 ± 2.4 vs 7.4 ± 3.1, $p < 0.001$). In a subgroup of 17 patients with LVOTO and ABPR who subsequently underwent successful myectomy, 5 (30%) demonstrated persistent ABPR. 23 patients (3.8%) experienced sudden cardiac death or ventricular arrhythmias, which were not associated with ABPR, regardless of age group. In multivariable analysis, syncope ($p = 0.04$), left ventricular hypertrophy ($p = 0.02$) and left atrial diameter ($p = 0.006$) were significantly associated with the composite outcome of sudden death or severe ventricular arrhythmia, whereas ABPR was not ($p = 0.38$). In contrast, ABPR was associated with subsequent heart failure hospitalization ($p = 0.002$), regardless of presence or absence of LVOTO ($p = 0.04$, $p = 0.02$).
Conclusions: ABPR is associated with reduced functional capacity in HCM regardless of the presence of LVOTO but is not associated with adverse arrhythmia outcomes. Patients with ABPR have a higher incidence of subsequent heart failure hospitalization.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is the most common monogenetic inherited heart condition. A major focus of clinical management in HCM is risk stratification for life-threatening ventricular arrhythmias. The current American Heart Association (AHA)/American College of Cardiology (ACC) guidelines rely on 5 primary risk factors for risk stratification: family history of sudden death at age < 40, syncope, non-sustained ventricular tachycardia (NSVT), maximum left ventricular wall thickness > 30 mm, and abnormal blood pressure response (ABPR) during exercise [1]. However, the European Society of Cardiology (ESC) guidelines recommend a more recently developed sudden cardiac death (SCD)-risk model that included left ventricular outflow tract obstruction (LVOTO), but did not include exercise test variables in its derivation [2,3].

Further complicating the assessment of risk associated with exercise hemodynamics in HCM is the unclear relationship between left ventricular outflow tract obstruction and ABPR. Some studies have ascribed ABPR to left ventricular outflow tract obstruction (LVOTO), but other studies did not show a relationship between LVOTO and ABPR [4–7]. Since the ESC SCD-risk model did not assess this relationship, the interaction between LVOTO and ABPR in predicting SCD remains unclear. The objectives of this study were to clarify the relationship between ABPR and LVOTO in

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a contemporary cohort of HCM patients, to relate these factors with the arrhythmic substrate in HCM, and to determine whether ABPR is independently associated with adverse outcomes in HCM.

2. Methods

This study was a retrospective single-center analysis of adult (age > 18 years) HCM patients who underwent baseline exercise stress testing and subsequent clinical follow-up. The study was approved by the institutional research review board. HCM was defined as in the ACC/AHA guidelines [1]. Infiltrative forms of hypertrophy were excluded. All eligible patients were identified from a prospective institutional HCM registry. Cardiopulmonary treadmill exercise stress tests were performed in the majority of patients (n = 434), with the remainder having had standard treadmill exercise stress tests (n = 155). ABPR was defined as a lack of rise of blood pressure during exercise of at least 20 mm Hg. This group was further subdivided as follows: 1) hypotensive ABPR was defined as a decrease >20 mm Hg from peak systolic blood pressure (SBP) or fall in SBP of >20 mm Hg at any point below resting SBP; and 2) blunted ABPR was defined as a rise in SBP of <20 mm Hg from resting to peak exercise not meeting criteria for hypotensive ABPR. These definitions were based on the criteria established by Sadoul et al. [8] LVOTO was defined as left ventricular outflow tract gradient >30 mm Hg at rest, with Valsalva, or immediately post-exercise. Left ventricular outflow tract gradient was measured at rest, with Valsalva and post exercise; the largest of these values was used for subsequent analyses that correlated the magnitudes of the gradient. Magnetic resonance imaging (MRI) delayed enhancement images for a subset of patients were quantified for amount of delayed enhancement using the 6-standard deviation (SD) method [9]. Two different outcome groups were analyzed to distinguish associations with both adverse arrhythmia outcomes and adverse heart failure outcomes. The adverse arrhythmia outcome included ventricular tachycardia (VT)/ventricular fibrillation (VF) arrest, sudden cardiac death, or appropriate implantable cardioverter-defibrillator (ICD) therapy. The adverse arrhythmia outcome was further sub-classified based on patient age < 40 years since one prior report found that ABPR was only associated with adverse arrhythmic outcomes in that subgroup [8,10,11]. The adverse heart failure outcome was first heart failure hospitalization. Only events occurring after the initial exercise stress test were considered.

2.1. Statistical methods

Descriptive data is presented as mean ± standard deviation. Continuous variables were compared using ANOVA with the Tukey post hoc test for comparisons of multiple groups when applicable. Categorical variables were compared using chi square. Survival analysis was performed using the Kaplan Meier method with Cox proportional Hazard model. Statistical analysis was performed with SPSS, Inc. (Chicago, IL).

3. Results

3.1. Baseline characteristics

A total of 589 patients met the study inclusion criteria. Baseline characteristics of the study population are displayed in Table 1.

Of 589 patients, 192 (33%) had an ABPR. Notably, in terms of disease severity metrics, maximum wall thickness was modestly increased in the ABPR group but left atrial volume and age at diagnosis were not different between groups. Gender was associated with ABPR, 27% (96) of males demonstrated ABPR whereas 42% (96) of females demonstrated ABPR ($p \leq 0.001$). LVOTO was not significantly associated with ABPR (56% vs. 63%, $p = 0.11$); however, patients with ABPR demonstrated greater left ventricular outflow tract gradients (35.7 mm Hg vs. 43.2 mm Hg $p = 0.030$). A smaller number of patients with a positive genetic test (43%, n = 68 vs. 59%, n = 97, $p = 0.011$) demonstrated ABPR.

For the subset of patients with MRI studies available (n = 363), there was no association between late gadolinium enhancement by MRI and ABPR ($p = 0.421$). LVOTO was associated with a lower likelihood of late gadolinium enhancement ($p = 0.05$).

Reproducibility of the blood pressure response was assessed in a subset of 222 patients who underwent subsequent exercise testing. Of 144 patients with an initial NBPR, 19% (n = 27) converted to ABPR on the subsequent test. Of 78 patients with an initial ABPR, 41 (52%) converted to NBPR on the subsequent test. In 12 of these 41 who converted from ABPR to NBPR, a successful surgical myectomy was performed in the interim, leaving a total of 29 (37%) that converted from ABPR to NBPR without any apparent cause. Medication changes in beta blockers and calcium channel blockers were reviewed for the 29 patients with ABPR to NBPR conversion, 16 (55%) patients had no change in medications, 7 (24%) had an interval dose increase and 6 (21%) had an interval dose decrease.

3.2. Relationship between LVOTO and ABPR

Although HCM with LVOTO was not more associated with ABPR than HCM without LVOTO in our overall patient cohort, we hypothesized that the cause and consequences of ABPR in those with and without LVOTO might be different. Therefore, we performed subgroup analysis of patients with ABPR either in the presence or absence of LVOTO. As shown in Fig. 1, ABPR was associated with diminished exercise capacity, as measured by percent of predicted max VO2, whether in the presence or absence of LVOTO ($p < 0.001$). In contrast, the percent of max predicted VO2 was not significantly different for those with LVOTO only, and METs achieved were more modestly reduced. Notably, the respiratory exchange ratio (RER), which is indicative of exercise effort, was similar among groups with normal blood pressure response (NBPR),

Table 1
Baseline characteristics.

Variable	Normal blood pressure response (n = 397)	Abnormal blood pressure response (n = 192)	p value	OR
Male	**265 (66.8%)**	**96 (50.0%)**	**<0.001**	**1.41–2.85 (2.01)**
Age at diagnosis (years)	45.7 ± 14.7	46.3 ± 16.5	0.642	
Age at exercise test (years)	50.0 ± 13.7	52.2 ± 14.2	0.062	
Genetic test positive	**97 (38.6%)**	**68 (52.3%)**	**0.011**	**1.13–2.67 (1.74)**
Max hypertrophy (mm)	**18.4 ± 4.5**	**19.6 ± 5.4**	**0.009**	
LA volume (mL)	93.7 ± 27.4	96.5 ± 32.2	0.286	
LVOT Obstruction	219 (55.9%)	120 (62.8%)	0.11	0.936–1.904 (1.33)
LVOT Gradient (mm Hg)	**35.7 ± 39**	**43.2 ± 39**	**0.030**	
Peak exercise BP (mm Hg)	**163 ± 25**	**130 ± 22**	**<0.001**	
End exercise BP (mm Hg)	**163 ± 25**	**123 ± 21**	**<0.001**	
Beta blocker and/or CCB	**272 (68.5%)**	**159 (82.8%)**	**<0.001**	**1.44–3.41 (2.21)**
VO2 max (% predicted)	**81.3 ± 23 (n = 295)**	**66.4 ± 21.5 (n = 139)**	**<0.001**	
METs	**8.0 ± 3.5 (n = 295)**	**5.4 ± 2.3 (n = 139)**	**<0.001**	
RER	**1.15 ± 0.1 (n = 295)**	**1.09 ± 0.1 (n = 139)**	**<0.001**	
LV mass MRI (grams)	141.8 ± 74 (n = 270)	142.1 ± 66 (n = 107)	0.971	
Fibrosis MRI	147 (56.5%)	63 (61.2%)	0.421	0.760–1.929 (1.21)
MRI 6 SD Mass	4.4 ± 9.0 (n = 68)	6.5 ± 13.9 (n = 46)	0.329	
History of NSVT	42 (10.6%)	31(16.1%)	0.055	0.987–2.68 (1.63)
NYHA Class 2–4	**148 (37.3%)**	**124 (64.6%)**	**<0.001**	**2.14–4.40 (3.07)**

LA: left atrium, LVOT: left ventricular outflow tract, BP: blood pressure, CCB: calcium channel blocker, MET: metabolic equivalent, RER: respiratory exchange ratio, LV: left ventricle, SD: standard deviation, NSVT: non-sustained ventricular tachycardia, NYHA: New York Heart Association. OR: odds ratio for X^2 test.
Bolded items indicate p < 0.05.

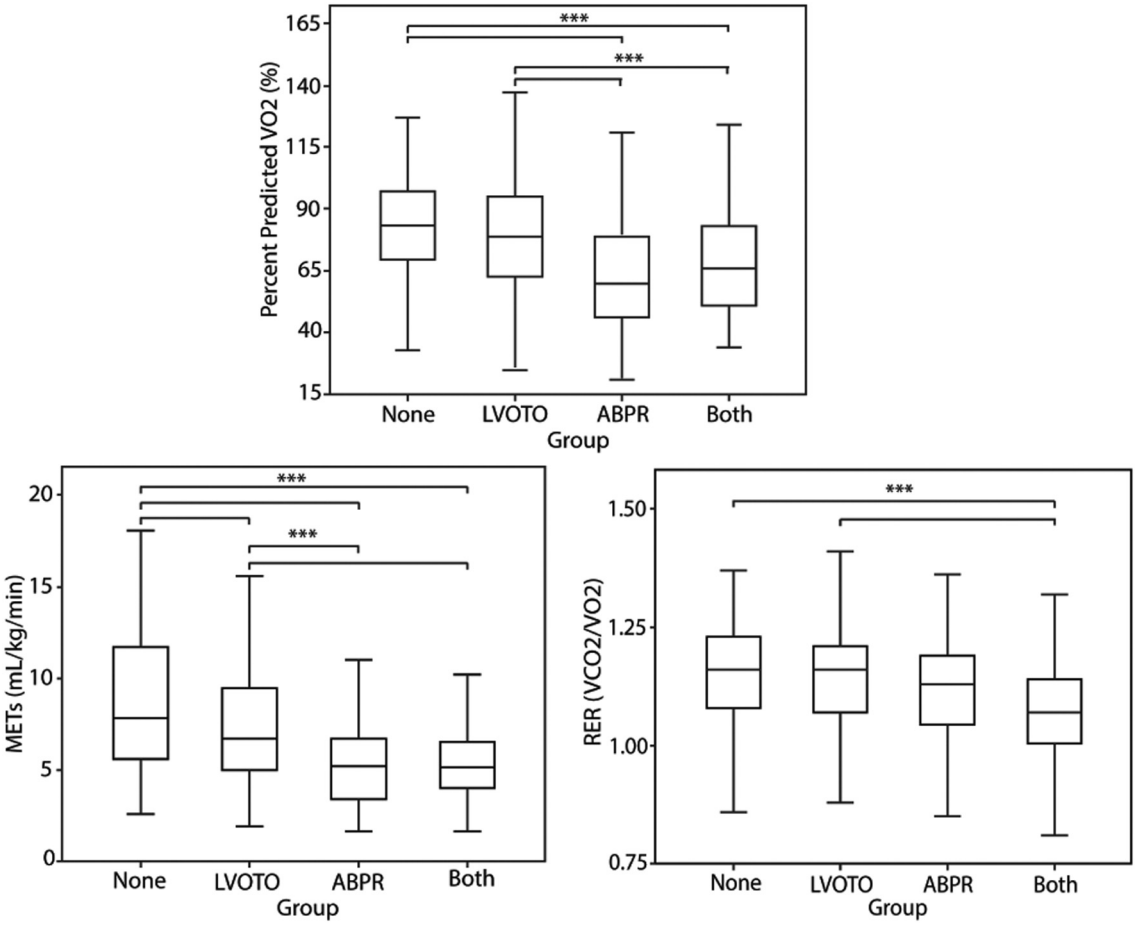

Fig. 1. Box plots of METs, percent predicted VO2, and RER for abnormal blood pressure response and left ventricular outflow tract obstruction groups showing mean, 1st and 3rd quartiles. Bars indicate groups with $p < 0.05$ for difference of mean. METs: metabolic equivalents, RER: respiratory exchange ratio, LVOTO: left ventricular outflow tract obstruction, ABPR: abnormal blood pressure response.

LVOTO only, and ABPR only, while it was modestly reduced in the subgroup with both LVOTO and ABPR.

To further understand the role of LVOTO on exercise hemodynamics in those with ABPR, a subgroup of patients with both LVOTO and ABPR who had undergone exercise stress test both before and after myectomy was examined (n = 17). All patients in this group demonstrated successful resolution of LVOTO following myectomy. However, 30% (n = 5) of these patients demonstrated persistent ABPR with exercise (2 blunted, 3 hypotensive), and consequently LVOTO was not significantly associated with resolution of ABPR following myectomy (Fisher's exact test, $p = 0.09$). Nevertheless, the peak systolic blood pressure in LVOTO patients who converted to NBPR following myectomy was greater than in patients without LVOTO who converted from ABPR to NBPR on a subsequent exercise test (42.5 ± 22.2 mm Hg vs. 17.3 ± 22.0 mm Hg, $p = 0.001$), suggesting an improvement in exercise hemodynamics beyond variability in the test itself. This finding suggests that, although LVOTO may have contributed to ABPR in some patients, it is also clearly coincidental to ABPR in a substantial proportion.

3.3. Hypotensive ABPR

Since a hypotensive blood pressure response to exercise is a markedly abnormal finding, we separately analyzed this subgroup (n = 82), see Table 2.

These patients had even further reduced exercise capacity (5.0 ± 2.2 METs, 64.4 ± 24.2% predicted of max VO_2). There was also no association between a hypotensive response and LVOTO in the group overall (55% with NBPR and LVOTO vs. 62% with hypotensive response and LVOTO, p = NS), indicating that LVOTO is clearly not the sole cause of a hypotensive ABPR. In 31 of the 82 (38%) patients with a hypotensive response, the hypotensive response required the exercise test to be stopped early (prior to achieving target heart rate or patient's perception of maximal effort) based on our institution's exercise safety protocol.

3.4. Survival/outcome analysis

In a mean follow-up time of 4.3 ± 3.3 years, there were 24 adverse arrhythmia outcomes and 25 adverse heart failure outcomes. Significant univariable predictors of adverse arrhythmia outcomes were left atrial size (HR 1.09 per mm [1.03–1.16], $p = 0.005$), history of NSVT (HR 3.44 [1.46–8.10], $p = 0.005$), history of syncope (HR 3.32 [1.23–8.94], $p = 0.018$), and maximum left ventricular hypertrophy (HR 1.1 per mm [1.042–1.17], $p = 0.002$). Age at evaluation and left ventricular outflow tract gradient were not significantly associated ($p = 0.881$ and $p = 0.981$). The adverse arrhythmia outcome was not associated with ABPR whether considering all ages ($p = 0.270$) or with restriction to patients <40 years old ($p = 0.708$). In contrast, patients with ABPR at baseline testing were more likely to have a subsequent heart failure hospitalization ($p = 0.002$). The presence or absence of LVOTO did not alter this association (LVOTO present $p = 0.041$, LVOTO absent $p = 0.018$). Notably, 5 patients who demonstrated ABPR and LVOTO and subsequently underwent myectomy with resolution of LVOTO were later hospitalized for heart failure (at a mean of 3.3 ± 2.0 years), indicating that ABPR in patients with LVOTO may still indicate risk of decompensated heart failure even after a successful myectomy. Kaplan-Meier survival curves for

Table 2
Hypotensive and blunted blood pressure response subgroups.

Variable	Normal blood pressure response (n = 397)	Hypotensive blood pressure response (n = 82)	p value	Blunted blood pressure response (n = 110)	p value
Male	**265 (66.8%)**	**40 (48.8%)**	**0.002**	**56 (50.9%)**	**0.002**
Age at diagnosis (years)	45.7 ± 14.7	47.9 ± 16	0.231	45.2 ± 16	0.745
Age at exercise test (years)	**50.0 ± 13.7**	**54.3 ± 13**	**0.010**	50.7 ± 14	0.608
Max hypertrophy (mm)	18.4 ± 4.5	19.3 ± 4.8 (n = 81)	0.120	**19.8 ± 5.8 (n = 108)**	**0.012**
LV EF	69 ± 6.8	68 ± 8.4	0.371	68.7 ± 8.1	0.560
LVIDd	45 ± 6.4 (n = 382)	44 ± 6.8 (n = 77)	0.202	44 ± 7.2 (n = 106)	0.072
LA diameter	**44 ± 7.0**	**46 ± 9.6**	**0.006**	**46 ± 7.0**	**0.020**
LA volume (mL)	93.7 ± 27.4	95.6 ± 34 (n = 81)	0.578	97.1 ± 31	0.276
LVOT obstruction	219 (55.9%)	51 (62.2%)	0.293	69 (63.3%)	0.165
LVOT gradient (mm Hg)	35.7 ± 39	42.0 ± 40	0.187	**44.1 ± 39 (n = 109)**	**0.047**
VO2 max (% predicted)	**81.3 ± 23 (n = 295)**	**64.4 ± 24.2 (n = 55)**	**<0.001**	**67.6 ± 19.6 (n = 84)**	**<0.001**
METs	**8.0 ± 3.5 (n = 295)**	**5.0 ± 2.2 (n = 55)**	**<0.001**	**5.7 ± 2.3 (n = 106)**	**<0.001**
RER	**1.15 ± 0.1 (n = 295)**	**1.07 ± 0.1 (n = 55)**	**<0.001**	**1.1 ± 0.1 (n = 84)**	**0.001**
LV mass MRI (g)	142 ± 74 (n = 270)	136 ± 74	0.649	146 ± 61 (n = 62)	0.659
MRI fibrosis	147 (56.5%)	27 (61.4%)	0.550	36 (61.0%)	0.530

LV: left ventricle, EF: ejection fraction, LVIDd: left ventricular internal diameter end diastole, LA: left atrium, LVOT: left ventricular outflow tract, MET: metabolic equivalent, RER: respiratory exchange ratio.
Bolded items indicate p < 0.05.

the combined arrhythmia outcome and for heart failure hospitalization are presented in Fig. 2. The survival curves for the adverse arrhythmia outcome were not significantly different between the NBPR group and the ABPR group ($p = 0.265$), and this relationship did not change for the subset of patients <40 years old ($p = 0.281$) or for the subset of patients with NYHA class >2 ($p = 0.882$). However, the survival analysis confirms that patients in the ABPR group were significantly more likely to undergo hospitalization for heart failure compared to those with NBPR ($p = 0.002$). When stratified by symptom burden, patients with NYHA class 3 or 4 symptoms and ABPR were more likely to undergo hospitalization for heart failure compared to those with NYHA class 3 or 4 symptoms and NBPR ($p = 0.017$). When this group was expanded to include patients with class 2,3 or 4 symptoms the association was no longer significant ($p = 0.115$).

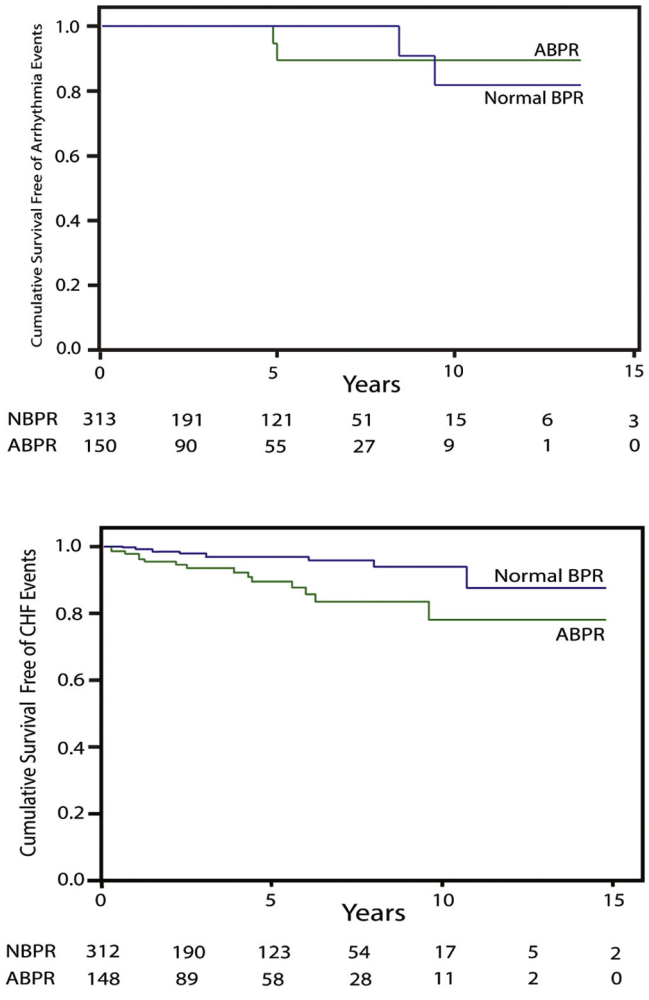

Fig. 2. Kaplan Meier survival curves for arrhythmia events and heart failure hospitalizations. NBPR: normal blood pressure response, ABPR: abnormal blood pressure response.

To compare risk estimation in our cohort to the validated ESC-HCM sudden death risk prediction model, we performed a Cox hazard regression using the variables present in the ESC-HCM model with the addition of ABPR. Statistically significant variables in the multivariable analysis from the ESC-HCM model in our cohort included a history of syncope (HR 3.25 [1.05–9.60], $p = 0.04$), left ventricular hypertrophy (HR 1.1 [1.02–1.18], $p = 0.02$), and left atrial diameter (HR 1.09 [1.02–1.16], $p = 0.006$). To completely rule out the possibility of variable interaction in the univariable analysis that would mask a true effect of ABPR, we also included ABPR in the multivariable model, and ABPR still was not significantly associated with risk ($p = 0.348$).

4. Discussion

Risk stratification for sudden cardiac death in patients with HCM remains a major challenge. Although ABPR remains in national guidelines in the U.S.A. as a major risk factor for SCD in HCM, the strength of evidence for a role of ABPR in clinical decision making is low [2,12]. A further complicating factor in the assessment of ABPR has been the unclear relationship with LVOTO. In this study, ABPR was not associated with ventricular arrhythmias or SCD, in contrast to more established risk factors. However, ABPR was strongly associated with reduced exercise capacity, and this association was independent of LVOTO. Furthermore, the ABPR group demonstrated a significantly greater likelihood of subsequent heart failure hospitalization, which was not altered by the presence or absence of LVOTO. Taken together, these findings support the concept that an ABPR is a clinical indicator of a lack of cardiac reserve, rather than a failure to increase systemic vascular resistance [13,14].

The complex interaction of LVOTO and ABPR has not been fully characterized. A subgroup of patients from this cohort with ABPR that underwent myectomy and resolution of LVOTO continued to demonstrate ABPR (30% of patients). This finding suggests that certain patients may demonstrate a mechanism of ABPR that is independent of LVOTO. Furthermore, among patients with LVOTO, an ABPR was associated with a diminished percent predicted VO2 max, similar to those with ABPR without LVOTO. Based on the subgroup with combined LVOTO

and ABPR who went on to surgical myectomy and had a follow-up exercise study, most patients with resolved LVOTO also converted to NPBR on the follow-up study. Therefore, the combination of LVOTO and ABPR may also identify patients who experience improved hemodynamics from directed treatment of LVOTO. ABPR was further subdivided into hypotensive and blunted groups since a hypotensive response to exercise is markedly abnormal. A blunted blood pressure response was associated with extent of left ventricular hypertrophy and magnitude of outflow gradient. A hypotensive response, despite being associated with even lower exercise tolerance, was not statistically significantly associated with extent of left ventricular hypertrophy or outflow tract gradient, but there was no significant difference between the blunted and hypotensive groups, and other markers of disease severity (Table 2) were similar between these subgroups. Many previous studies have not made the distinction between blood pressure response types, and the limited number of subjects in the hypotensive subgroup in this study limit the ability to make firm conclusions regarding risk estimation in this subgroup.

Prior studies have reported that ABPR indicates an increased risk of SCD, especially in patients <40 years old [6,15,16]. Accordingly, the ACC/AHA guidelines include ABPR as a major risk factor for SCD, and a single major risk factor has been considered sufficient to justify ICD implantation [1]. Several recent large studies have not included ABPR in their risk analyses, including studies of MRI delayed enhancement and the well-validated study used to derive the HCM-ESC risk score that is now in standard clinical practice [3,17]. Clarification of the potential role of ABPR is therefore critical, particularly since a large proportion of HCM patients demonstrate ABPR (33% in this cohort) [18]. A systematic review of risk stratification in HCM reports the most recent six studies that evaluated ABPR in relation to sudden cardiac death and shows four of these studies revealed no association [12]. The findings of these previous four studies are similar to the data presented in the current study as demonstrated by the survival curve in Fig. 2. Furthermore, of the two studies that did demonstrate an association between ABPR and death, one included deaths due to heart failure rather than only sudden cardiac death [6]. Our findings, in the context of these other studies, strongly support the removal of ABPR from risk estimation of SCD in HCM.

While ABPR was not associated with an increased risk of SCD it is was associated with an increased risk of heart failure admissions (Fig. 2). This fact, together with the association of ABPR, decreased exercise capacity and NYHA class, suggests that ABPR is an important prognostic variable in HCM, even though it is not directly associated with SCD. Patients with ABPR may be more likely to demonstrate clinical symptoms, suffer greater limitations due to their disease and require more frequent hospitalization. This finding highlights the current lack of any validated risk prediction model for heart failure in HCM, since the primary focus has traditionally been on SCD. ABPR may be useful to identify patients who are at risk of progression to heart failure and may require closer monitoring or intervention.

This study has some limitations. It is a retrospective observational study and cannot definitively identify causality of associations. The population was limited to a single center. The available patient data were retrospective and therefore subject to selection bias, although all patients were included from a prospectively generated institutional registry. To our knowledge no study has evaluated reproducibility of exercise blood pressure response in HCM patients. In our cohort, blood pressure response was reproducible; however, there was some crossover between groups with repeat testing, only some of which could be explained by an interval surgical myectomy. This may introduce some variability in outcome associations. Our institution's exercise safety protocol mandates that a hypotensive blood pressure response requires the exercise test to be stopped (regardless of heart rate attained or patient's perception of maximal effort), possibly explaining the lower RER in this subgroup. It is possible that some of these patients could have reached a somewhat higher exertion level if not limited — however, our general experience is that these patients are often markedly limited on a symptomatic basis. We did not withdraw cardioactive medications prior to exercise testing, as some other reports on the abnormal blood pressure response have done, since we use the results of exercise testing on medical therapy to guide clinical decision-making. Medication changes were reviewed for the subset of patients that converted from ABPR to NBPR; the majority of these patients were on stable to increased dose of beta blocker or calcium channel blocker at their repeat exercise stress test. Medication status did not significantly change the outcome of the Cox proportional hazard model or the Kaplan Meier survival analysis for heart failure hospitalizations or arrhythmia events. Lastly, blood pressures were measured supine and immediately post exercise, for this reason patients with ABPR occurring in the recovery phase would not have been recognized. Overall the proportion with an ABPR in our cohort was similar to prior reports.

5. Conclusion

ABPR is not predictive of SCD or ventricular arrhythmias and should not be used for decision-making regarding future arrhythmia risk. However, ABPR may be a useful parameter to identify patients at risk of heart failure who may benefit from closer monitoring or intervention. This study also highlights the need for future studies to analyze predictors of heart failure as a separate adverse outcome in HCM.

Conflict of interest

Eric Smith, June Tome, Ryan Mcgrath, Suwen Kumar, Maryann Concannon, Sharlene Day, Sara Saberi and Adam Helms report no relationships that could be interpreted as a conflict of interest.

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