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ORIGINAL RESEARCH

PEDIATRIC CARDIOLOGY

Cardiopulmonary Exercise Testing in Pediatric Patients With Hypertrophic Cardiomyopathy

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ABSTRACT

BACKGROUND Exercise stress testing (EST) in pediatric hypertrophic cardiomyopathy (HCM) patients has not well described in a large heterogenous cohort.

OBJECTIVES The objective of the study was to determine the clinical utility of EST in pediatric HCM.

METHODS This was a retrospective single-center analysis of HCM patients younger than 21 years who had EST between January 1, 2000, and January 1, 2019. Clinical, demographic characteristics, and EST data were analyzed, using the last EST during the study or prior to the event in subjects with a primary outcome. The primary composite endpoint included cardiac death, transplant, or arrhythmia requiring implantable cardioverter-defibrillator placement. Outcome analysis was performed using Cox proportional hazard modeling.

RESULTS The study cohort included 140 patients, 52% with a recognized genetic variant. There were 2 tests aborted due to safety concerns (ST-segment changes, ventricular ectopy). The median age at first EST was 13.6 years. Ninety percent of patients were tested using cycle ergometry, and 44% were on a beta-blocker. The median peak oxygen consumption was 37.1 mL/kg/min (IQR: 12.5 mL/kg/min) or 81.2% predicted, the mean anaerobic threshold was 21.8 Ml (IQR: 8.3 mL), and the median peak power was 2.6 $\pm$ 1.1 W/kg or 73.7% predicted. Ectopy during EST was seen in 44% of patients, and 8% had an abnormal blood pressure response to exercise. The endpoint was reached in 12 patients. The presence of any degree of ectopy was a predictor of the composite endpoint (hazard ratio: 5.8; 95% CI: 1.3-26.7).

CONCLUSIONS EST is clinically useful in select pediatric patients with HCM. Ectopy on EST is a risk factor for cardiac death, cardiac transplant, and arrhythmias requiring implantable cardioverter-defibrillator. (JACC Adv 2022;1:100107)

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ABBREVIATIONS AND ACRONYMS

ABPR = abnormal blood pressure response

EF = ejection fraction

EST = exercise stress test

HCM = hypertrophic cardiomyopathy

HR = hazards ratio

ICD = implantable cardioverter-defibrillator

LA = left atrial

SCD = sudden cardiac death

VO_2 = maximal oxygen consumption

Hypertrophic cardiomyopathy (HCM) is the most common inherited form of pediatric cardiomyopathy with an incidence of 0.47 per 100,000 children[1,2] and is characterized by a heterogenous collection of clinical phenotypes.[3] While the majority of patients with HCM have a relatively benign course[4], the disease can also be characterized by malignant arrythmias, progressive heart failure, and sudden cardiac death (SCD).[5] As such, there have been several efforts to evaluate risk factors for mortality in children with HCM, with degree of hypertrophy, unexplained syncope, and nonsustained ventricular tachycardia all shown to be predictive of SCD.[6-9]

In the adult population, there has been a recent focus on the utility of serial exercise stress testing (EST) in patients with HCM, with studies showing that subnormal measures of gas exchange, including maximal oxygen consumption (VO_2) and ventilatory inefficiency, are associated with reduced survival,[10-13] and the recently updated American Heart Association guidelines recommend EST as a component of the clinical evaluation.[14] In children, however, EST has not been universally incorporated into the standard of care[15], and with the exception of noting the negative prognostic implications of a failure in the ability to augment blood pressure response,[7] the utility of EST in pediatric patients with HCM is largely unknown.

Thus, the purpose of this study is to describe EST in pediatric HCM patients performed at a single center over the course of an 18-year period, with a focus on exercise performance compared to normative values, changes in exercise performance with increasing age, and findings on EST predictive of adverse cardiac outcomes.

METHODS

This study was performed with approval from the Children's Hospital of Philadelphia Institutional Review Board. Written informed consent was waived owing to the retrospective nature of the study.

COHORT SELECTION. This was a single-center retrospective observational cohort study. Participants were included in our study if they had a diagnosis of HCM, underwent EST at the Children's Hospital of Philadelphia between January 1, 2000, and January 1, 2019, and were younger than 21 years at the time of testing. The standard of care at our center is to refer all patients with a diagnosis of HCM for EST, unless they are physically unable to participate in testing. Potential cases were identified by querying the Exercise Physiology Laboratory Database for patients coded as HCM. Each participant's medical record was reviewed to confirm the diagnosis of HCM. All patients included in this study were classified as phenotype positive by their primary cardiologist. Patients who were described as possible HCM, or who were genotype positive/phenotype negative, were not included in the study cohort. Subjects meeting the primary endpoint (defined below) prior to their first EST were excluded.

DATA COLLECTION. Demographic and clinical information was collected by manual review of the electronic medical record, including age at HCM diagnosis and first EST, history of genetic diagnosis, cardiac procedures and medications, arrhythmia leading to intervention, and SCD.

Data collected from review of EST reports included maximal VO_2 and VO_2 at the anaerobic threshold, heart rate response, blood pressure response, and presence of exercise-associated ectopy or ST-segment changes during EST. The presence of any ectopic beats, either atrial or ventricular, during warmup, exercise, or recovery was defined as ectopy. An abnormal blood pressure response (ABPR) was defined as the failure to augment the systolic blood pressure during exercise by at least 20 mm Hg. Data from echocardiograms, including left ventricular ejection fraction (EF), septal wall thickness, and left ventricular outflow tract obstruction, were collected from clinical reports. Imaging studies performed within 3 months prior to or 1 month after EST were included. For those with multiple tests, descriptive statistics were captured from either the most recent EST within the study window or the most recent EST prior to reaching the primary outcome.

Follow-up information through April 1, 2019, was included, as well as clinical history preceding initial EST. Data from both inpatient and outpatient clinical records were included.

CLINICAL OUTCOME. The primary study endpoint was a composite outcome of SCD, aborted SCD, transplant, or ventricular arrhythmia prompting implantable cardioverter-defibrillator (ICD) placement, with each subject limited to a single outcome. If a patient had 2 outcomes separated in time (ie, an aborted SCD followed by transplant), the initial event was selected as the outcome. The components of the composite outcome were chosen based on their similar underlying biologic mechanisms. Patients

TABLE 1 Demographics of Patients With and Without a Primary Outcome

	All (N = 140)	Patients Without a Primary Outcome (n = 128)	Patients With a Primary Outcome (n = 12)	*P* Value[a]
Race, n (%)				0.04
Non-Hispanic White	98 (70.0)	93 (72.7)	5 (41.7)	
Non-Hispanic Black	35 (25.0)	29 (22.7)	6 (50.0)	
Other	7 (5.0)	6 (4.6)	1 (8.3)	
Male, n (%)	112 (80.0)	103 (80.5)	9 (75.0)	0.70
Age at diagnosis of HCM (y)	12.0 (8.0)	12.0 (8.0)	12.0 (6.0)	0.63
Age at the first EST (y)	13.6 (5.1)	13.8 (5.2)	13.4 (4.0)	0.50
Age at the last EST (y)[b]	15.9 (4.3)	16.0 (4.5)	15.3 (2.5)	0.85
Year difference between the first EST and endpoint/last EST	1.1 (3.4)	1.1 (3.3)	1.1 (5.7)	0.53
Pathogenic genetic change identified, n (%)	73 (52.1)	65 (50.8)	8 (66.7)	0.29
Genetic change identified (n = 73), n (%)				
Possibly pathogenic mutation	19 (26.0)	17 (26.2)	2 (25.0)	1.00
Known pathogenic mutation	54 (74.0)	48 (73.8)	6 (75.0)	
Subjects with a single EST during the study period, n (%)	55 (39.3)	49 (38.3)	6 (50.0)	0.53
Subjects with >2 y between first and follow-up EST, n (%)	54 (38.6)	48 (37.5)	6 (50.0)	0.53

Values are median (IQR) unless otherwise indicated. [a]*t*-tests, chi-square tests, or Fisher exact tests were used to compare patients with no end point reached vs patients with end point. [b]Either the last test in subjects without end point or the last test prior to end point.

EST = exercise stress test; HCM = hypertrophic cardiomyopathy.

with no follow-up visits after their first EST during the study period were defined as lost to follow-up.

STATISTICAL ANALYSIS. Clinical and demographic characteristics were summarized using median (IQR) for continuous variables and percentage for categorical variables. EST data analysis was performed using the last EST completed within the study window or the last test prior to the event in subjects with a primary outcome. Percent predictive values were determined based on previously published normative values.[16] Demographics and clinical characteristics were compared between those patients without end point reached vs those patients with end point using *t*-test, Mann-Whitney *U* test, chi-square test, and Fisher exact test. To describe the EST characteristic change across age, mixed-effects regression models with fractional polynomial functions were used adjusting for the presence of a maximum effort test, to describe either linear or curvilinear associations.[17] A total of 164 models with the dimension of the fractional polynomial up to 3 (m = 3, chosen by the plotted data and sensitivity analysis up to 4 dimension) were tested for each EST characteristic, and the parsimonious polynomial models were determined by the function selection procedure in STATA (StataCorp LLC), that is, selecting the simpler model with the lowest Bayesian information criterion, which indicated a better fit than other models.[18,19] LOWESS (Locally Weighted Scatterplot Smoothing) plots of predicted mean and 95% CIs across age were presented with scatter plots.

To examine the demographic and EST characteristics associated with the primary outcome, separate Cox proportional hazards models were used for each characteristic. Separate models were used for EST variables due to collinearity. Selection of candidate factors associated with the primary outcome was determined based on clinical suspicion. Beta-blocker use was adjusted in the Cox model of peak heart rate. The assumption of proportional hazards over time was satisfied by testing the statistical significance of predictors by time interaction effects in the model and plotting the Schoenfeld residuals. Hazard ratios and 95% CIs are presented. Kaplan-Meier analysis was used to examine the survival rates stratified by the presence or absence of ectopy on EST. The log-rank test was used to test the difference between survival curves. Statistical analysis was performed using SAS version 9.4 (SAS Institute) and STATA version 15.

RESULTS

DEMOGRAPHICS AND CLINICAL CHARACTERISTICS. Over the 18 years studied, 140 patients with HCM who underwent at least 1 EST were identified. Seventy percent of the cohort was white (n = 98), 80% were male (n = 112), and slightly over one-half (52.1%, n = 73) had an identified pathogenic or potentially pathogenic mutation at the time of testing (Supplemental Table 1). The median age of HCM diagnosis was 12.0 years, and the median age at first EST was 13.6 years (**Table 1**).

TABLE 2 Clinical and Echocardiographic Characteristics in Patients With and Without a Primary Outcome

	All (N = 140)	Patients Without a Primary Outcome (n = 128)	Patients With a Primary Outcome (n = 12)	*P* Value[a]
Cardiac medications at time of most recent EST (n = 140), n (%)	64 (45.7)	55 (43.0)	9 (75.0)	0.03
Beta-blocker	61 (43.6)	52 (40.6)	9 (75.0)	0.02
Calcium channel blocker	4 (2.9)	4 (3.1)	0 (0.0)	1.00
Disopyramide	4 (2.9)	4 (3.1)	0	1.00
Matched echocardiogram (n = 116)				
Age at the selected echo	15.7 (4.3)	15.8 (4.4)	15.3 (2.5)	0.96
Month difference between EST and matched echocardiogram	0 (0.05)	0 (0)	0.0 (0.2)	0.73
LVEF (n = 90)	68.0 (8.0)	68.0 (8.0)	74.0 (18.0)	0.18
LVEF <55% (n = 90), n (%)	0 (0)	0 (0)	0 (0)	1.00
Septal max diameter (cm) (n = 113)	1.4 (1.0)	1.4 (0.8)	1.9 (1.6)	0.02
Septal maximal Z score (n = 106)	2.9 (5.9)	2.9 (5.8)	4.7 (7.2)	0.17
Posterior wall diameter (cm) (n = 112)	1.1 (0.4)	1.1 (0.4)	1.4 (0.7)	0.004
Posterior wall Z score (n = 107)	1.9 (2.6)	1.8 (2.7)	2.8 (2.4)	0.03
LVOT gradient peak >20 mm Hg (n = 105), n (%)	30 (28.6)	25 (26.6)	5 (45.5)	0.28

Values are median (IQR) unless otherwise indicated. Reflects the echocardiogram performed closest temporally to EST, at most 3 months prior to or 1 month after EST. There are 26 subjects who did not have matched echo data to the defined EST cases in table. [a]*t*-Tests, Mann-Whitney *U* test, chi-square tests, or Fisher exact tests were used to compare patients with no end point reached vs patients with end point.

EST = exercise stress test; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract.

Beta-blockers were prescribed at the time of most recent EST in nearly one-half of all patients (43.6%, n = 61). Echocardiographic data were available for 116 patients and showed a median EF of 68.0% and a median maximum septal wall thickness of 1.4 cm. There were no patients in the study with depressed left ventricular function (EF <55%), and 28.6% of patients had a peak left

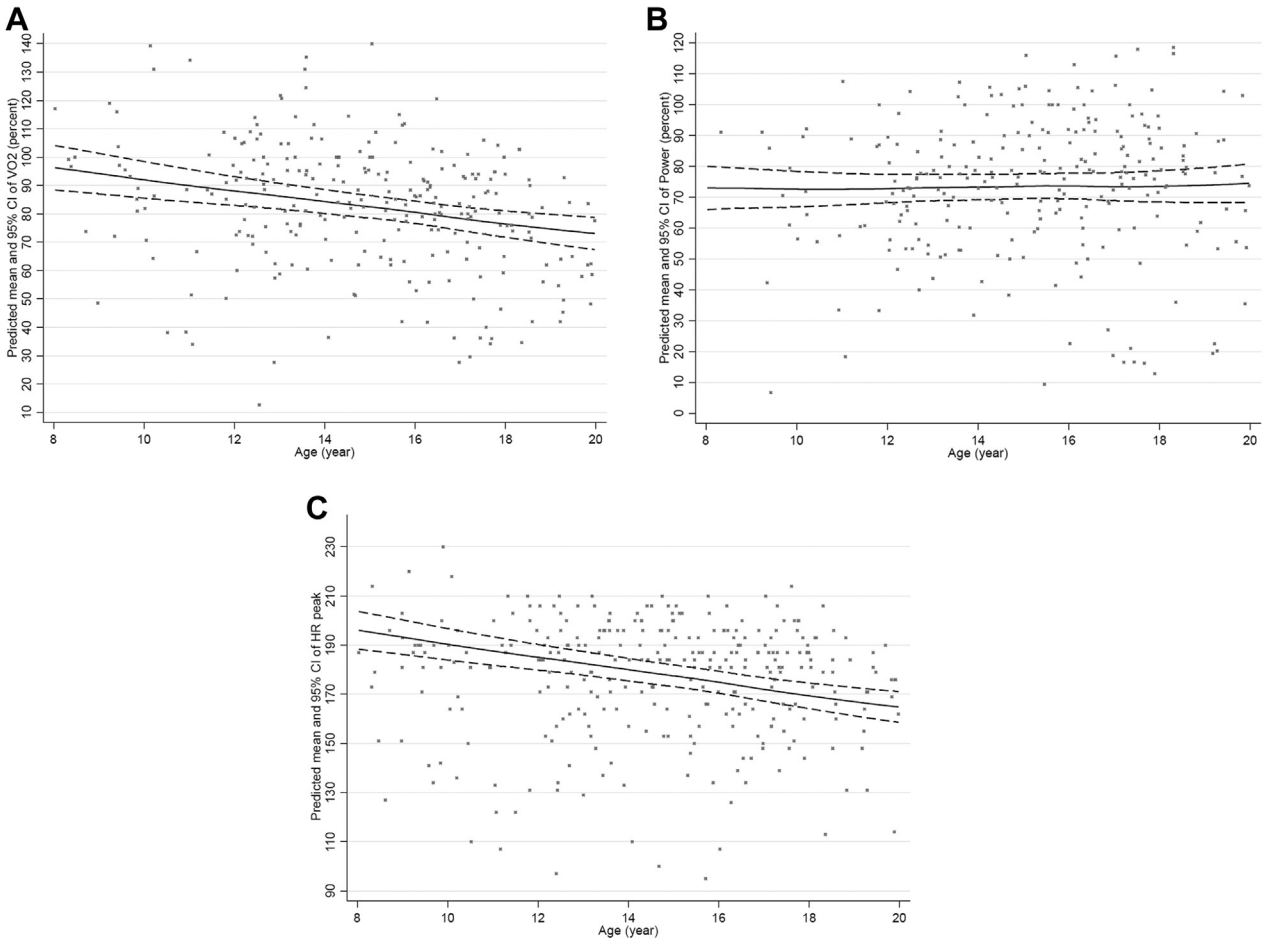
TABLE 3 Exercise Stress Test Data in Patients With and Without a Primary Outcome

	All (N = 140)	Patients Without a Primary Outcome (n = 128)	Patients With a Primary Outcome (n = 12)	*P* Value[a]
Age at EST (y) (n = 140)	15.9 (4.3)	16.0 (4.5)	15.3 (2.5)	0.85
Height at EST (cm) (n = 139)	168.0 (16.5)	168.0 (17.0)	170.2 (11.1)	0.39
Weight at EST (kg) (n = 140)	65.5 (27.2)	64.2 (26.4)	85.2 (29.5)	0.02
EST mode (n = 135), n (%)				
Bike	122 (90.4)	111 (90.2)	11 (91.7)	1.00
Treadmill	13 (9.6)	12 (9.8)	1 (8.3)	
Maximum effort test (n = 139), n (%)	110 (79.4)	101 (79.5)	9 (75.0)	0.71
VO_2 (mL/kg/min)[b] (n = 126)	37.1 (12.5)	37.8 (12.7)	30.5 (16.7)	0.27
VO_2 (mL/min) (n = 133)	2162.0 (1260.0)	2196.5 (1315.0)	1896.0 (1150.0)	0.75
VO_2 (% predicted) (n = 126)	81.2 (28.6)	81.2 (28.8)	79.5 (20.2)	0.46
AT (mL) (n = 110)	21.8 (8.3)	22.0 (8.3)	20.2 (7.1)	0.16
AT (% peak VO_2) (n = 114)	60.7 (12.4)	59.0 (12.4)	63.4 (7.8)	0.47
Power (W) (n = 124)	147.0 (98.0)	147.5 (102.0)	131.0 (102.0)	0.82
Power (W/kg)[a] (n = 118)	2.6 (1.1)	2.6 (1.0)	2.2 (1.1)	0.24
power (% predicted) (n = 118)	73.7 (30.2)	74.2 (29.4)	63.0 (30.0)	0.27
Heart rate at rest (n = 140)	68.0 (18.0)	68.0 (18.0)	66.0 (17.5)	0.52
Heart rate, peak (n = 140)	181.0 (28.0)	182.5 (26.0)	160.5 (42.5)	0.24
Heart rate reserve[c] (n = 140)	136.0 (20.5)	136.0 (21.0)	138.5 (13.5)	0.45
Ectopy during testing (n = 140), n (%)	61 (43.6)	51 (39.8)	10 (83.3)	0.003
ST-segment changes during the test (n = 98), n (%)	27 (27.6)	24 (26.7)	3 (37.5)	0.68
RER >1.2 (n = 133), n (%)	83 (62.4)	76 (62.3)	7 (63.6)	1.00
Abnormal BP response to exercise (n = 136), n (%)	11 (8.1)	11 (8.8)	0 (0)	0.59

Values are median (IQR) unless otherwise indicated. Data reflect either the last test in the study window for subjects without the end point or the last test prior to the end point in those reaching one. [a]*t*-tests, chi-square tests, or Fisher exact tests were used to compare patients with no end point reached vs patients with end point. [b]Adjusted to ideal body weight in subjects with BMI >95 percentile. [c]Heart rate reserve = maximum heart rate − resting heart rate.

AT = anaerobic threshold; BMI = body mass index; BP = blood pressure; EST = exercise stress test; RER = respiratory exchange ratio; VO_2 = peak oxygen uptake.

FIGURE 1 **Exercise Stress Test Characteristics by Age**



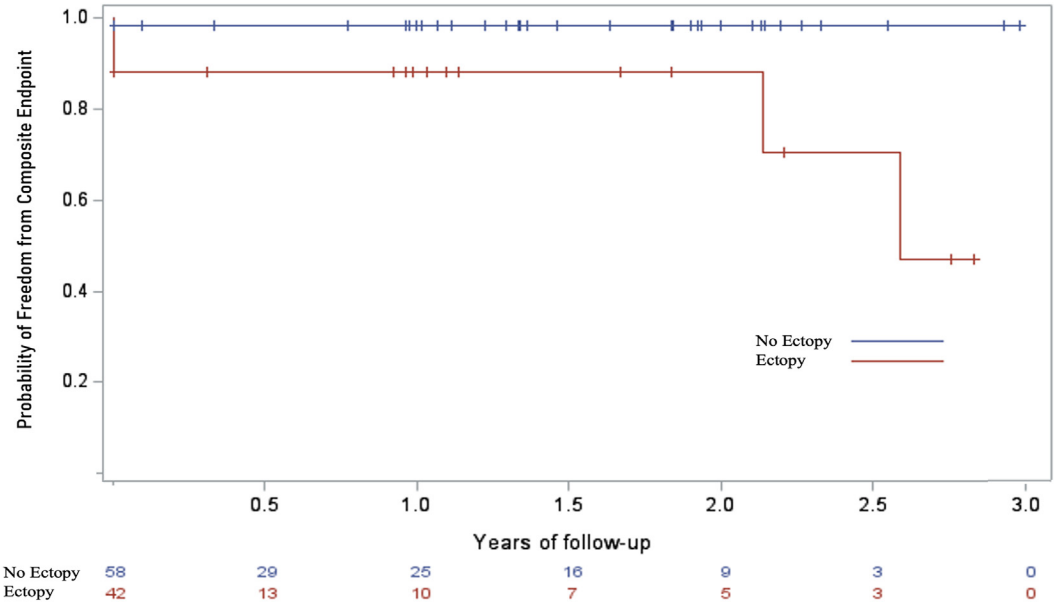
(A) In children with hypertrophic cardiomyopathy, peak oxygen consumption decreased with increasing age, suggesting a progressive decline in cardiorespiratory fitness. The best fit model was defined as, VO_2 (% predicted) = 116.33 to 2.15 × age, after adjusting for maximum effort test. *P* value of age < 0.001. **(B)** There was no change in peak power consumption with increasing age. The best fit model was defined as, power (% predicted) = 78.63−age × 0.18, after adjusting for maximum effort test. *P* value of age = 0.70. **(C)** Peak heart rate decreased with increasing age. The best fit model was defined as peak HR = 222.39 to 2.86 × age after adjusting for maximum effort test. *P* value of age < 0.001. VO_2 = peak oxygen consumption.

ventricular outflow tract gradient of >20 mm Hg (n = 105) (Table 2).

EXERCISE CAPACITY IN PATIENTS WITH HCM. Most patients (90.4%, n = 122) were tested using ramp cycle ergometry, and 79.4% (n = 110) had a maximum effort test. When analyzing 1 EST per subject (either last in study window or last prior to primary outcome event), the median VO_2 was 37.1 ml/kg/min, or 81.2% predicted. The median anaerobic threshold was 21.8 ml/kg/min, and the median peak power was 2.6 W/kg, or 73.7% predicted. Forty-three percent (n = 61) of subjects had ectopy documented during exercise. Ectopy was defined broadly, with any ectopic beats, either atrial or ventricular, during warmup, exercise, or recovery included. The type and timing of ectopy among all 12 patients who met the composite outcome is more completely characterized in Supplemental Table 2. There were 11 patients (8.2%) who had an ABPR (Table 3).

EXERCISE CAPACITY WITH INCREASING AGE. EST data from 140 subjects (age ranging from 8 to 20 years) with 301 ESTs were used to evaluate changes in maximal VO_2, power, and peak heart rate on serial tests as patients aged. Figures 1A to 1C show the trajectories of these measurements and respective 95% CIs. While there was no significant change in percent predicted power with age, there was a

FIGURE 2 Probability of Meeting the Composite Endpoint in Pediatric Patients With Hypertrophic Cardiomyopathy Stratified According to Those With and Without Ectopy on Exercise Stress Testing



Freedom from the primary composite outcome over 3 years of follow-up. Years of follow-up was defined by the difference between age at the first exercise stress testing and age at the outcome/last exercise stress testing. The log-rank test $P = 0.01$.

significant decrease in percent predicted VO_2 and maximum heart rate as age increased (both $P < 0.001$).

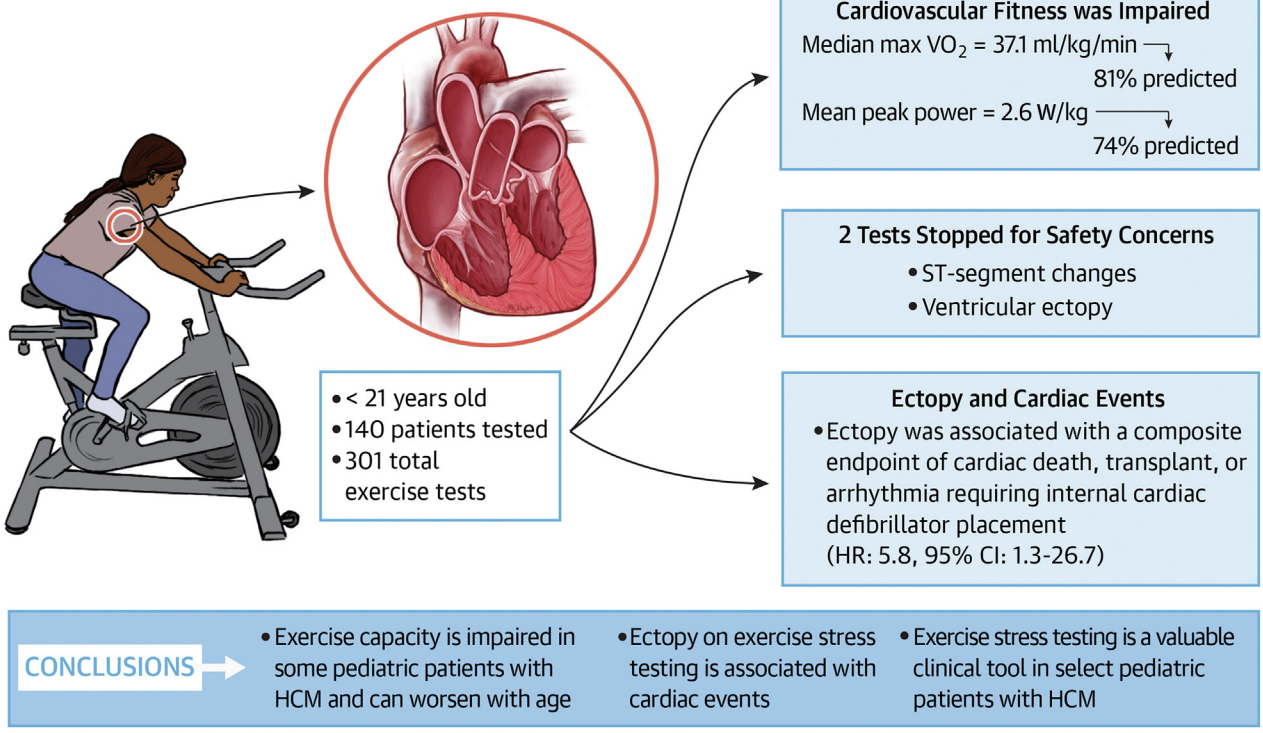
FACTORS ASSOCIATED WITH THE PRIMARY ENDPOINT. The primary composite outcome was reached in 12 of the 140 patients (8.6%), including 2 subjects with cardiac death, 3 with aborted cardiac death, 2 who underwent heart transplant, and 7 subjects with ventricular arrhythmia leading directly to ICD placement. The time from EST to event varied greatly, ranging from 1 day to >1 year. None of the patients who had ectopy on EST were immediately referred for ICD placement, rather some of those patients had them implanted at a later date for a variety of reasons. Freedom from the composite outcome was significantly greater in the no-ectopy group as seen in Figure 2 (log-rank test $P = 0.01$). Ectopy during testing was associated with the compositive outcome (HR: 5.8; 95% CI: 1.3-26.7). Neither impaired exercise tolerance nor an abnormal blood pressure response during EST was predictive of the composite outcome (Central Illustration, Tables 4 and 5).

DISCUSSION

To the best of our knowledge, this is the largest description of EST in pediatric patients with HCM and has several notable findings relevant to the evaluation and management of this patient population. In this select pediatric population with HCM, EST was rarely stopped for safety concerns. Overall, exercise performance was impaired and declined with increasing age, which has important prognostic and therapeutic implications. Finally, ectopy during EST was associated with a composite outcome of death, transplant, or arrhythmia requiring ICD placement.

SAFETY OF EST IN HCM. Historically, there have been reservations about the use of EST in HCM patients due to concerns about arrhythmic or hemodynamic risk.[5] Many studies of adults with HCM have since demonstrated the feasibility and safety of EST when performed in a controlled setting[11,13] and guidelines emphasize its clinical utility as well as the value of recreational exercise.[20] In this study, which included 301 ESTs in 140 select pediatric patients with HCM, <1% (n = 2) were stopped for safety concerns. One of these tests showed increasing ST-segment depression that was not accompanied by symptoms, and the other was stopped in the setting of ventricular ectopy. There were no episodes of sustained arrhythmia, hemodynamic collapse, or cardiac arrest, and no studies were stopped early for chest pain, presyncopal symptoms, or syncope. These data

CENTRAL ILLUSTRATION **Cardiopulmonary Exercise Testing in Pediatric Patients with Hypertrophic Cardiomyopathy**



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suggest that EST can be performed in carefully selected patients without significant risk of adverse events; however, it should be done in a setting that includes close monitoring by practitioners knowledgeable in pediatric cardiomyopathy, electrophysiology, and exercise physiology. EST may be helpful in identifying those patients with HCM who are good candidates for an at-home exercise prescription or who can exercise safely with a shared risk decision model. Importantly, these data do not indicate that exercise testing is safe in all children with HCM as patients who were sent for EST in the retrospective study may have been preselected by clinicians such that those at highest risk were not referred for an EST.

EXERCISE PERFORMANCE IN HCM. This study shows that, overall, cardiovascular fitness was impaired in this cohort of pediatric patients with HCM and that it declines with age. Peak VO_2 represents the maximum volume of oxygen consumed by the body and is a useful measure of cardiorespiratory fitness in a healthy child.[10,12,13,21-23] Previous studies have demonstrated impaired exercise function in adults with HCM and have shown that reduced peak VO_2 is predictive of total mortality and progression to advanced heart failure or heart transplant. In our study population, peak VO_2 and power were reduced when compared to normative values, and the inverse correlation of peak VO_2 and age suggests these

TABLE 4 Exercise Stress Test Characteristics in Patients With a Primary Outcome

	Composite Outcome (n = 12)	Cardiac Death, Aborted Cardiac Death, or Transplant (n = 5)	Ventricular Arrhythmia (n = 7)
Low VO_2 (% predicted)[a]	2/11 (18%)	1/5	1/6
Low AT[a]	4/10 (40%)	2/4	2/6
Low AT (% peak VO_2)[a]	1/10 (10%)	0/4	1/6
Low power (% predicted)[a]	3/11 (27%)	2/5	1/6
Heart rate, peak <175 beats/min[b]	7/12 (58%)	3/5	4/7
Abnormal BP response to exercise	0/11 (0%)	0/5	0/6
Ectopy during testing	10/12 (83%)	5/5	5/7
ST-segment changes during the test	3/8 (38%)	1/3	2/5

P value not available as the separate events were not mutually exclusive. [a]Defined as less than the 25th percentile of subjects. 25th percentile values: VO_2% predicted = 65.0%, AT = 17.6 mL, AT (% peak VO_2) = 54.3%, power % predicted = 59.0%. [b]Adjusting for beta-blocker use.

AT = anaerobic threshold; BP = blood pressure; VO_2 = peak oxygen uptake.

TABLE 5 Factors Associated With the Primary Outcome (Cardiac Death, Transplant, and Arrhythmia Prompting ICD)[a]

Demographic	
Race (reference: non-Hispanic White)	
Non-Hispanic Black	**3.4 (1.0-11.1), $P = 0.04$**
Other	2.1 (0.2-19.4), $P = 0.49$
Male	1.0 (0.3-3.6), $P = 0.94$
Age at diagnosis of HCM <2 y	0.7 (0.2-3.5), $P = 0.70$
Genetic diagnosis	1.3 (0.4-4.4), $P = 0.66$
Maximum effort test	0.9 (0.2-3.5), $P = 0.91$
EST data	
Low VO_2 (% predicted)[b]	0.2 (0.0-1.8), $P = 0.16$
Low AT[b]	1.6 (0.4-6.4), $P = 0.50$
Low AT (% predicted)[b]	0.5 (0.1-3.9), $P = 0.49$
Low power (% predicted)[b]	0.5 (0.1-2.4), $P = 0.38$
Heart rate, peak <175[c]	0.8 (0.2-3.0), $P = 0.68$
Abnormal BP response to exercise	NA
Ectopy during testing	**5.8 (1.3-26.7), $P = 0.02$**
ST-segment changes during testing	1.3 (0.3-5.5), $P = 0.72$

Values are HR (95% CI). **Bold** values indicate the statistically significant result. [a]Separate Cox proportional hazards models were used for each characteristic. [b]Defined as less than the 25th percentile of subjects. 25th percentile values: VO_2% predicted = 65.0%, AT = 17.6 mL, AT (% peak VO_2) = 54.3%, power % predicted = 59.0%. [c]Cox model was adjusted for beta-blocker use.

AT = anaerobic threshold; BP = blood pressure; EST = exercise stress test; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; VO_2 = peak oxygen uptake.

patients have worsening exercise function as they age. While several studies have shown that heart failure symptoms are predictive of adverse outcomes in children with HCM,[1,24] a recent risk prediction model for SCD in children with HCM did not include heart failure symptoms in their determination of risk.[25] This discrepancy may be due to the difficulty in eliciting and identifying heart failure symptoms in children, and EST may be an alternative method to identify previously unrecognized functional limitations. While impaired performance on EST was not predictive of adverse outcomes in our cohort, this may be because the study was underpowered for relatively rare outcomes and deserves further evaluation in a larger cohort. Aside from potential implications on outcomes, this finding is further concerning in light of the known correlation between reduced activity and psychosocial wellbeing[26,27] and the possibility that activity restrictions have come with the unintended consequence of increasing the cardiovascular risk profile in a population already with risk factors in place.[28-30]

RISK FACTORS IDENTIFIED BY EST. Our study demonstrates that EST may provide information helpful for cardiac risk stratification for children with HCM. Ectopy of any kind, including isolated premature atrial or ventricular contractions, correlated with the composite outcome of SCD, transplant, or ventricular arrhythmia prompting ICD placement; 10 of 12 children who reached the primary outcome had ectopy on EST. While previous studies have shown nonsustained ventricular arrhythmia as a risk factor for SCD in young people with HCM[6,25] and that, in adults, atrial fibrillation during EST predicts poor outcomes,[31] our finding that exercise-induced atrial or ventricular ectopy is associated with outcomes is a novel finding and further highlights the utility of EST in this population. Left atrial (LA) size, a marker of impaired diastolic function, is a known risk factor for SCD in both children and adults. We hypothesize that atrial ectopy, which was found to be associated with adverse outcomes, may be more commonly seen in children with LA dilation and LA hypertension, a physiology which can be provoked during exercise.

It is also important to note that of the 80 patients who had no ectopy during testing, none of them died, had SCD, or were transplanted, and only 2 of that group ultimately had ventricular tachycardia which led to ICD placement. Thus, the absence of ectopy on EST may help in identifying a group of patients at lower risk.

These findings have several important clinical implications. First, they suggest that patients with ectopy on EST may deserve closer monitoring with more frequent outpatient follow-up and ambulatory rhythm monitoring. Second, they suggest that patients with no ectopy on EST may be a lower risk cohort and, therefore, might be reasonable candidates for a shared decision-making model for athletic participation. However, other clinical variables must also be integrated into risk stratification in these patients.

ABPR has previously been cited as a risk factor for SCD in children[7]; no such predictive association was seen in our study group. Decker et al[7] used treadmill testing and the modified Bruce protocol, a technique that can make accurate assessment of blood pressure difficult. The majority of our cohort was tested using cycle ergometry with direct auscultation of blood pressure, which produces less artifact and, we believe, provides a more reliable result. The findings in this study further support the recently updated HCM guidelines which have removed ABPR as part of the routine evaluation of SCD risk.[14]

Further work evaluating the relationship between exercise capacity and symptoms, quality of life, and outcomes in children with HCM is needed. A better understanding could aid in the difficult process of forming exercise guidelines, which traditionally have taken a conservative approach despite consensus that exercise positively impacts cardiovascular and overall health and evidence that inactivity is prevalent in patients with HCM.[27,32] If decreased aerobic capacity portends worse

outcomes in these patients, the balance of risk vs benefit regarding exercise may change. Thus, EST may serve as an integral tool in the process of "shared decision-making" around exercise introduced in the most recent American Heart Association guidelines.[14]

STUDY LIMITATIONS

This study has limitations intrinsic to retrospective analysis, and the findings may differ from a prospectively enrolled cohort. Our study did not include a control group. Our center is a tertiary referral center that may see a greater portion of severe HCM, and some patients were referred from smaller centers and thus had limited follow-up. Given that the focus of this study was on exercise testing, not all conventional risk factors for SCD were evaluated. The composite outcome was rare, and the study may not be powered to detect all risk factors. As a consequence, a multivariable analysis of risk factors for the primary outcome could not be performed. While this study adds to the literature on the value of EST in children with HCM, limitations exist due to the small numbers of patients and events and the possible selection bias of patients undergoing EST.

CONCLUSIONS

Exercise capacity may be impaired in pediatric patients with HCM and can worsen with age. EST is a valuable clinical tool to assess exercise capacity in this population. Ectopy on EST is associated with the composite outcome of SCD, cardiac transplant, and arrhythmias requiring ICD. These findings suggest that EST is useful in the care of pediatric patient with HCM.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Ectopy during EST is associated with cardiac death, transplant, and need for ICD placement in pediatric patients with HCM EST provides valuable information about exercise capacity, which can be impaired in this population. Testing can be performed in select pediatric patients but should be done in a setting that includes close monitoring by practitioners knowledgeable in pediatric cardiomyopathy and electrophysiology. Data collected through EST can aid in the process of shared decision-making between providers and patients with HCM when discussing the risks and benefits of exercise.

TRANSLATIONAL OUTLOOK: Longer follow-up in pediatric patients with HCM, with EST performed at standardized and more frequent intervals, will provide more information about change in exercise capacity with increasing age. Greater analysis into subgroups, such as by sex, race, or genetic diagnosis, should be undertaken to better describe fitness in each group and shape exercise recommendations with greater precision.

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