Circulation

ORIGINAL RESEARCH ARTICLE

The Prevalence and Association of Exercise Test Abnormalities With Sudden Cardiac Death and Transplant-Free Survival in Childhood Hypertrophic Cardiomyopathy

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BACKGROUND: Hypertrophic cardiomyopathy (HCM) can be associated with an abnormal exercise response. In adults with HCM, abnormal results on exercise stress testing are predictive of heart failure outcomes. Our goal was to determine whether an abnormal exercise response is associated with adverse outcomes in pediatric patients with HCM.

METHODS: In an international cohort study including 20 centers, phenotype-positive patients with primary HCM who were <18 years of age at diagnosis were included. Abnormal exercise response was defined as a blunted blood pressure response and new or worsened ST- or T-wave segment changes or complex ventricular ectopy. Sudden cardiac death (SCD) events were defined as a composite of SCD and aborted sudden cardiac arrest. Using Kaplan-Meier survival, competing outcomes, and Cox regression analyses, we analyzed the association of abnormal exercise test results with transplant and SCD event-free survival.

RESULTS: Of 724 eligible patients, 630 underwent at least 1 exercise test. There were no major differences in clinical characteristics between those with or without an exercise test. The median age at exercise testing was 13.8 years (interquartile range, 4.7 years); 78% were male and 39% were receiving beta-blockers. A total of 175 (28%) had abnormal test results. Patients with abnormal test results had more severe septal hypertrophy, higher left atrial diameter *z* scores, higher resting left ventricular outflow tract gradient, and higher frequency of myectomy compared with participants with normal test results ($P<0.05$). Compared with normal test results, abnormal test results were independently associated with lower 5-year transplant-free survival (97% versus 88%, respectively; $P=0.005$). Patients with exercise-induced ischemia were most likely to experience all-cause death or transplant (hazard ratio, 4.86 [95% CI, 1.69–13.99]), followed by those with an abnormal blood pressure response (hazard ratio, 3.19 [95% CI, 1.32–7.71]). Exercise-induced ischemia was also independently associated with lower SCD event-free survival (hazard ratio, 3.32 [95% CI, 1.27–8.70]). Exercise-induced ectopy was not associated with survival.

CONCLUSIONS: Exercise abnormalities are common in childhood HCM. An abnormal exercise test result was independently associated with lower transplant-free survival, especially in those with an ischemic or abnormal blood pressure response with exercise. Exercise-induced ischemia was also independently associated with SCD events. These findings argue for routine exercise testing in childhood HCM as part of ongoing risk assessment.

Key Words: cardiomyopathy, hypertrophic ■ death, sudden, cardiac ■ defibrillators, implantable ■ exercise test ■ pediatrics

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This manuscript was sent to Marc Cribbs, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material, the podcast, and transcript are available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.122.062699.

For Sources of Funding and Disclosures, see page 727.

Circulation is available at www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- In an international multicenter study of 630 pediatric patients with hypertrophic cardiomyopathy, 28% had abnormalities during exercise stress testing.
- An abnormal exercise test result was independently associated with lower 5-year transplant-free survival, particularly for patients with an abnormal blood pressure response or exercise-induced ischemia.
- Exercise-induced ischemia was also associated with the risk of sudden cardiac death events.

What Are the Clinical Implications?

- Routine exercise testing has clinical usefulness in assessing risk of adverse events for children with hypertrophic cardiomyopathy.
- Patients with an abnormal blood pressure response or exercise-induced ischemia should be monitored for the development of heart failure and for risk of sudden cardiac death to enable timely interventions.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
CPET	cardiopulmonary exercise testing
HCM	hypertrophic cardiomyopathy
HR	hazard ratio
ICD	implantable cardioverter defibrillator
LA	left atrial
LV	left ventricular
LVOTO	left ventricular outflow tract obstruction
LVPWD	left ventricular posterior wall diameter
PRIMaCY	Precision Medicine for Cardiomyopathy
SCA	sudden cardiac arrest
SCD	sudden cardiac death

Hypertrophic cardiomyopathy (HCM) is the most common childhood cardiomyopathy. Clinical manifestations can range from asymptomatic to the occurrence of major adverse cardiac events, such as sudden or aborted sudden cardiac death (SCD) and heart failure. Recent years have seen the development of risk prediction models for SCD in pediatric patients with HCM that rely primarily on symptoms and echocardiographic findings.[1,2] Current risk prediction models for SCD or transplant-free survival do not incorporate exercise test results.

Small, single-center studies that focused on cardiopulmonary exercise testing (CPET) have shown, in univariable analyses, that the percentage of predicted peak oxygen consumption (Vo_2) has a strong association with heart failure mortality and SCD in pediatric HCM.[3] In adults, the role of exercise stress testing has been further delineated. CPET measures, incorporated into prediction models, have been useful in determining risk of heart failure, SCD, and stroke-related events.[4] However, in recent adult HCM studies, peak Vo_2 was associated primarily with heart failure and transplant, rather than with SCD.[5,6] The 2020 American Heart Association and American College of Cardiology clinical practice guidelines recommend exercise stress testing, or, in some cases, exercise stress echocardiography, primarily to assess provocable left ventricular outflow tract obstruction (LVOTO) and to assess functional capacity, whereas CPET is recommended primarily to guide decision-making for advanced therapies in those with nonobstructive HCM and symptomatic heart failure.[7]

CPET is not routinely available at all centers. Treadmill or bicycle exercise testing without measurement of gas exchange is used more commonly to assess abnormal heart rate, blood pressure (BP), ischemic or arrhythmic response to exercise, and functional capacity. Despite its widespread use, large studies investigating the clinical usefulness of exercise testing in predicting major adverse cardiac events in pediatric patients with HCM are lacking.

The objectives of this study were to determine whether an abnormal exercise response is associated with SCD events and transplant-free survival in childhood HCM, as well as which type of abnormal response (abnormal BP response, ischemia, or ectopy) is associated with these outcomes.

METHODS

Data Statement

The data that support the findings of this study are available from the corresponding authors upon reasonable request. Corresponding authors had full access to all the data in the study and take responsibility for its integrity and the data analysis.

Study Cohort

PRIMaCY (Precision Medicine for Cardiomyopathy) is an international observational cohort study of pediatric patients with HCM followed at 20 tertiary-care cardiomyopathy centers (15 US, 4 Canadian, and 1 Australian). Cohort details have been published previously.[1] Phenotype-positive primary patients with HCM who were <18 years of age at the time of first evaluation who underwent a treadmill or bicycle exercise stress test as part of clinical care (with or without cardiopulmonary exchange) were eligible for this study. Phenotype-positive was defined as septal or posterior wall thickness >2 SD above mean for body surface area on echocardiographic imaging in patients clinically diagnosed with HCM. Primary HCM was defined as isolated HCM without secondary causes of left ventricular (LV) hypertrophy (such as hypertension, metabolic or mitochondrial disease, major structural heart disease, syndromes, or neuromuscular disorders). The study was

approved by the research ethics board at each participating institution, and waiver of consent was obtained.

Demographic characteristics, exercise test reports, echocardiographic measures, and clinical outcomes (death, cause of death, cardiac transplant, interventions, including implantable cardioverter defibrillator [ICD] use, and appropriate ICD discharges) on follow-up were collected through retrospective chart review. Echocardiographic data were captured within ±12 months of the first exercise test. Transplant-free survival was defined as survival free of any cause of death or heart transplant. SCD was defined as death within 1 hour of sudden cardiac arrest (SCA). Aborted SCA was defined as resuscitated SCA in which subsequent interventions restored cardiac output. An SCD event was defined as the composite of SCD and aborted SCA.

An abnormal exercise test result was defined as the first exercise test that showed the presence of ≥1 of the following abnormalities on clinical tests reported by cardiologists or exercise physiologists: an abnormal BP response (ie, failure to increase systolic BP by ≥20 mm Hg or a drop in systolic BP during exercise),[7] ischemia (ie, new or worsening ST- or T-wave changes during exercise), complex ventricular ectopy (eg, frequent single premature ventricular contractions, ventricular couplets, ventricular bigeminy, or >3 consecutive premature ventricular contractions, or a combination) during exercise or recovery. If ischemia or ectopy occurred in conjunction with an abnormal BP response, the abnormalities were classified under the abnormal BP response category. A blunted heart rate response alone was not considered abnormal because of a high prevalence of beta-blocker use in patients undergoing exercise testing, which can blunt chronotropic response to exercise. A provocable LV outflow tract gradient on exercise echocardiography alone was not included as an abnormal response for the purpose of this study because this information was only available in a subset of patients who underwent exercise echocardiography. The exercise abnormalities reported were adjudicated by consensus between 2 independent investigators. In addition, a random sampling of exercise reports was obtained from participating sites to verify the interpretation captured in the database.

Echocardiographic data captured within ±12 months of the index exercise test were compared across subgroups and included interventricular septal diameter *z* score, LV posterior wall diameter (LVPWD) *z* score, end-systolic left atrial (LA) diameter *z* score, LV ejection fraction, and the presence of LVOTO (ie, resting peak LV outflow tract gradient >30 mm Hg on quantitative assessment or moderate or greater obstruction on qualitative assessment). The chamber diameters were quantified using Boston *z* scores. Site principal investigators re-reviewed echocardiograms to capture missing data when feasible using standardized measurements.

Statistical Analysis

Categorical variables were described as frequencies and proportions, and continuous variables were summarized as median and interquartile range or mean and SD. Proportions were compared using χ^2 or Fisher exact test, medians were compared using Wilcoxon rank-sum test, and means were compared using Student *t* test. All time to event analyses were censored at 5 years. Kaplan-Meier survival analyses for time to event from the first exercise test, log-rank test, and Cox proportional hazard regression were used to compare normal and abnormal exercise test groups. Analyses were further stratified by type of exercise test abnormality (ie, abnormal BP response, ischemia, or ectopy). The 5-year survival and incidence rate of events per 100 person-years were assessed between groups. Patients with an SCD event or transplant before the exercise test were excluded from the respective survival analyses.

In the subset of patients with complete echocardiographic parameters, Cox proportional hazard regression was used to determine the association of abnormal exercise test and other risk factors with survival using a multivariable model. Factors analyzed included age at exercise testing, history of unexplained syncope, nonsustained ventricular tachycardia, interventricular septal diameter *z* score, LVPWD *z* score, and presence of LVOTO.

Competing risk models were used to quantify the cumulative incidence of SCD and the competing risk from death of other causes or transplant grouped by normal and abnormal test results. The between-group difference in cumulative incidence function was evaluated using Gray tests. All statistical analyses were performed in Stata software version 16 and R software version 4.0.3. A *P* value <0.05 was considered statistically significant.

RESULTS

Study Cohort

Of 724 phenotype-positive patients in the PRIMaCY cohort, 630 patients underwent at least 1 exercise test after first clinical evaluation at a participating site. Figure S1A shows the number of serial exercise tests across patients. Figure S1B shows the number of patients with exercise tests at each participating site, and Figure S1C shows the same data in patients >8 years of age (ie, those old enough to perform an exercise test). The data show that a majority (69%) of eligible patients underwent an exercise test across sites. Table 1 outlines the characteristics of all the patients who underwent an exercise test. The median age at exercise testing was 13.8 years (interquartile range, 4.7) and the majority were male (75%). When compared with patients >8 years of age who had not undergone an exercise test, those who underwent exercise testing had a lower frequency of aborted SCA, less LVOTO, lower frequency of myectomy, and higher frequency of nonsustained ventricular tachycardia on Holter monitor ($P<0.05$; Tables S1 and S2).

Of the 630 patients who underwent an exercise test, 28% (n=175) met the criteria for an abnormal exercise test result. The most common exercise abnormality was an abnormal BP response (61%) followed by ischemia (22%) and ectopy (17%). Table 1 shows patient characteristics between those with normal and abnormal exercise test results. There were small differences in age at testing, sex, and genotype status between the 2 groups ($P<0.05$). A higher proportion of patients with an abnormal exercise test result had surgical myectomy ($P=0.001$). On echocardiography, those with an abnormal exercise test result had a

Table 1. Clinical Characteristics of Patients With Normal or Abnormal Exercise Testing

Variable	Overall (n=630)	Exercise test normal (n=455)	Exercise test abnormal (n=175)	*P* value	Age at event, y, median (IQR)
Abnormal exercise categories, n (%)					
Blood pressure response			106 (61)		
Ectopy			30 (17)		
Ischemia			39 (22)		
Male, n (%)	473 (75)	357 (78)	116 (66)	0.002	
Age at first evaluation, y, median (IQR)	12.58 (5.99)	12.81 (5.94)	12.20 (6.82)	0.040	
Age at exercise test, y, median (IQR)	13.81 (4.76)	14.15 (4.72)	12.99 (4.55)	0.003	
Race, n (%)					
White	328 (52)	221 (49)	107 (61)	0.001	
Black or African American	48 (8)	46 (10)	2 (1)		
Asian	30 (5)	14 (3)	16 (9)		
Mixed	4 (1)	2 (0.4)	2 (1)		
Other	6 (1)	4 (1)	2 (1)		
Unknown	214 (34)	168 (37)	46 (26)		
Family history, n (%)					
HCM	304 (48)	222 (49)	82 (47)	0.663	
SCD	122 (19)	95 (21)	27 (15)	0.121	
History of SCD in first-degree relatives	35 (6)	22 (5)	13 (7)	0.203	
Medical history, n (%)					
Beta-blocker use during first exercise test	248 (39)	175 (38)	73 (42)	0.690	
History of syncope	65 (10)	46 (10)	19 (11)	0.782	
NSVT (on Holter)	76 (12)	54 (12)	22 (13)	0.808	
Myectomy	60 (10)	32 (7)	28 (16)	0.001	
Genotype, n (%)					
Positive	243 (39)	161 (35)	82 (47)	0.003	
Negative	185 (29)	131 (29)	54 (31)		
Unknown	202 (32)	163 (36)	39 (22)		
Outcomes/intervention, n (%)					
Aborted SCA	46 (7)	28 (6)	18 (10)	0.074	14.25 (5.2)
ICD insertion	242 (38)	142 (31)	100 (57)	<0.001	14.54 (4.18)
Primary	197 (31)	115 (25)	82 (47)	<0.001	14.53 (4.07)
Secondary	45 (7)	27 (6)	18 (10)	0.057	14.87 (3.56)
Appropriate shock for any ICD	28 (4)	10 (2)	18 (10)	<0.001	15.37 (5.24)
Deaths					
Sudden cardiac death	9 (1)	5 (1)	4 (2)	0.261	15.17 (5.68)
Death from other cause	7 (1)	5 (1)	2 (1)	0.962	15.21 (3.97)
Transplant	18 (3)	5 (1)	13 (7)	<0.001	14.31 (4.36)

HCM indicates hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; IQR, interquartile range; NSVT, nonsustained ventricular tachycardia; SCA, sudden cardiac arrest; and SCD, sudden cardiac death.

higher mean interventricular septal diameter *z* score (*P*=0.001), higher LA diameter *z* score (*P*<0.001), higher LV ejection fraction (*P*=0.035), and higher frequency of LVOTO (*P*=0.003; Table 2).

In the overall cohort, 46 (7%) experienced aborted SCA, 9 (1%) experienced SCD, 7 (1%) died from other causes, and 18 (3%) underwent a heart transplant on follow-up. ICD insertion and appropriate ICD discharges were more frequent in those with an abnormal exercise test result (*P*<0.001).

All-Cause Mortality or Transplant

Patients with an abnormal exercise test result had lower 5-year freedom from all-cause mortality or transplant (from the time of the index exercise test) compared with those with normal test results (88% versus 97%,

Table 2. Echocardiographic Characteristics of Patients With Normal or Abnormal Exercise Testing

Echocardiographic measures*	Number ascertained	Overall	Number ascertained	Exercise test normal	Number ascertained	Exercise test abnormal	*P* value
IVSd *z* score, mean (SD)	569	10.30 (9.15)	404	9.50 (9.03)	165	12.24 (9.18)	0.001
LVPWd *z* score, mean (SD)	569	3.11 (4.14)	402	2.98 (3.45)	167	3.41 (5.47)	0.266
LA diameter *z* score, mean (SD)	431	1.21 (1.66)	290	0.94 (1.65)	141	1.76 (1.55)	<0.001
LVEF, mean (SD)	407	72.27 (10.03)	283	71.58 (9.46)	124	73.85 (11.1)	0.035
LV outflow tract obstruction, n %	542	101 (19)	377	58 (15)	165	43 (26)	0.003

IVSd indicates interventricular septal diameter; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; and LVPWd, left ventricular posterior wall diameter.

*Measured within ±12 months of exercise test.

respectively; *P*=0.005; Figure 1A), with a hazard ratio (HR) for all-cause mortality and transplant of 2.97 (95% CI, 1.34–6.55; *P*=0.007).

On subgroup analysis, 5-year transplant-free survival varied by type of abnormal exercise response (*P*=0.0016; Figure 1B). The rate of all-cause mortality or transplant was 4.6 per 100 person-years in the ischemia category, 2.89 per 100 person-years in the abnormal BP response category, and 0.93 per 100 person-years in those with normal exercise test results. Patients with ventricular ectopy as the only exercise-induced abnormality did not experience any events. Compared with those with normal exercise testing, there was a significantly higher hazard of all-cause mortality or transplant in those with an abnormal BP response (HR, 3.19 [95% CI, 1.32–7.71]; *P*=0.010) and in those with an ischemic response (HR, 4.86 [95% CI, 1.69–13.99]; *P*=0.003).

A multivariable analysis was performed in a subset of 465 patients who had complete echocardiographic data. An abnormal exercise test result was an independent predictor of all-cause mortality or transplant (HR, 3.27 [95% CI, 1.33–8.05]; *P*=0.010), as was a higher LVPWD *z* score with a higher HR, for every unit increase in *z* score (HR, 1.09 [95% CI, 1.01–61.18]; *P*=0.021; Table 3). Because LA diameter and LV ejection fraction were missing in >20% of the cohort, these variables were not included in the model.

SCD Events

We further analyzed freedom from SCD events (composite of SCD or aborted SCA) by type of exercise response. Overall, there was no difference in the 5-year freedom from SCD events between those with normal versus abnormal exercise test results (94% versus 88%; *P*=0.22; Figure 2A). However, on subgroup analysis, 5-year SCD event-free survival varied by type of abnormal exercise response (*P*=0.007; Figure 2B). In those with ischemia, the rate of SCD was 5.89 events per 100 person-years compared with 1.7 events per 100 person-years for those with an abnormal BP response and 1.41 events per 100 person-years for those with normal exercise test results. There were no events in patients with ventricular ectopy on exercise testing. Compared with those with normal exercise testing results, the hazard of an SCD event was significantly higher in the ischemia category (*P*=0.004) but not in the abnormal BP response category (*P*=0.676). On multivariable analysis, exercise-induced ischemia remained independently associated with SCD event-free survival (HR, 3.32 [95% CI, 1.27–8.70]; *P*=0.014).

In light of more appropriate ICD discharges in patients with an abnormal exercise test result, we did a secondary analysis in the subset who had primary prevention ICD implantation after an exercise test was performed (n=165). Five-year freedom from appropriate ICD discharges was lower in those with an abnormal exercise test result (n=69) compared with those with normal exercise test results (n=96; 85% versus 97% respectively; *P*=0.032; HR, 3.86 [95% CI, 1.02–14.5]; Figure 2C). When compared by exercise response category, there was a higher hazard of appropriate shocks in those with exercise-induced ischemia (HR, 5.83 [95% CI, 0.97–35.0]; *P*=0.054) and in those with ectopy (HR, 5.7 [95% CI, 0.95–34.1]; *P*=0.056) compared with those with a normal exercise test result, but these differences were not statistically significant (Figure 2D). This analysis was limited by the small number of events in each subgroup.

Other Deaths or Transplant

Survival was also assessed after excluding those with SCD before transplant. Those with an abnormal exercise test result had a lower freedom from other deaths or transplant compared with those with a normal exercise test result (91% versus 98%, respectively; *P*=0.004; Figure 3A). Survival varied by type of exercise abnormalities (*P*=0.004), with the highest event rate in those with exercise-induced ischemia (4.6 events per 100 person-years). The HR for other deaths or transplant for those with an ischemic response was 7.64 (95% CI, 2.4–24.1; *P*=0.001), and for those with an abnormal BP response, the HR was 3.33 (95% CI, 1.1–9.9; *P*=0.031; Figure 3B).

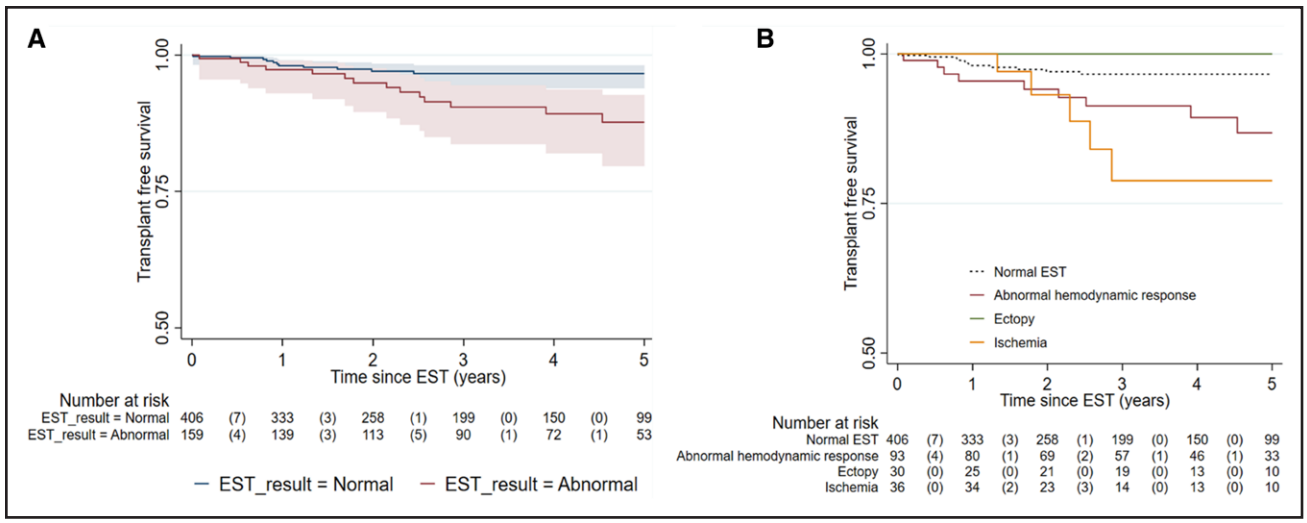

Figure 1. All-cause mortality or transplant.
A, Kaplan-Meier analysis showed that, compared with those with normal exercise stress test (EST) results (n=406; blue), 5-year transplant-free survival (all-cause mortality or transplant) was lower in those with an abnormal exercise test result (n=159; red; 97% vs 88%; *P*=0.005 by log-rank test). **B**, Kaplan-Meier analysis showed a difference in transplant-free survival by type of exercise-induced abnormality (*P*=0.0016). Compared with those with normal EST results (dashed black), 5-year transplant-free survival was lower for those with exercise-induced ischemia (orange; 79%; hazard ratio, 4.86 [95% CI, 1.69–13.99]; *P*=0.003) and those with an abnormal blood pressure response (red; 87%; hazard ratio, 3.19 [95% CI, 1.32–7.71]; *P*=0.01). There were no deaths or heart transplants in the exercise-induced ectopy-only category (green).

Competing Outcomes

Cumulative incidence function was used to quantify the cumulative proportion of events from the first normal or abnormal exercise test result. The 5-year cumulative proportion of death or transplant from the exercise test was significantly higher among patients with abnormal compared with normal test results (8.9% versus 2.3%; *P*=0.004; Figure 4A). On competing outcomes analysis, the 5-year cumulative incidence of SCD was not different between those with an abnormal versus a normal exercise test result (3.4% versus 1.1%, respectively; *P*=0.48). However, the 5-year cumulative incidence of other causes of death or transplant remained higher for those with abnormal versus normal test results (8.9% versus 2.3%, respectively; *P*=0.004; Figure 4B and 4C).

Table 3. Risk Factors Associated With All-Cause Mortality and Transplant

Variables	Hazard ratio	95% CI	*P* value
Abnormal exercise test result	3.27	1.33–8.05	0.010*
Age at exercise test	0.95	0.83–1.09	0.454
Unexplained syncope	1.38	0.39–4.85	0.616
Nonsustained ventricular tachycardia	1.26	0.41–3.88	0.684
IVSd *z* score	1.00	0.96–1.05	0.891
LVPWd *z* score	1.09	1.01–1.18	0.021*
LV outflow tract obstruction	0.38	0.09–1.63	0.193

IVSd indicates interventricular septal diameter; LV, left ventricular; and LVPWd, left ventricular posterior wall diameter.
*Significant.

DISCUSSION

In one of the largest multicenter analyses of exercise testing in pediatric HCM, we found that more than one-quarter of children and adolescents (28%) had an abnormality detected on exercise testing, and that an abnormal exercise test result was independently associated with lower transplant-free survival, driven primarily by a higher transplant event rate. Novel to this study is the association of individual exercise abnormalities with outcomes, with exercise-induced ischemia emerging as the factor most strongly associated with both transplant-free survival and SCD events.

There are no practice guidelines for the role of exercise stress testing in the assessment and follow-up of children with HCM. In adults, the use of exercise testing has shifted primarily toward assessing for provocable LV outflow tract gradients and to the use of CPET for assessing functional capacity in those with advanced heart failure, rather than to predict SCD.[7,8] We know that risk factors for SCD in children with HCM can differ from those of adults. Hence, we evaluated the association of exercise test findings with both transplant-free survival and SCD in this pediatric cohort. We found that an abnormal exercise test result in children with HCM was independently associated with lower transplant-free survival, with the strongest association seen in patients with an ischemic response followed by those with an abnormal BP response to exercise. In addition, exercise-induced ischemia was also independently associated with SCD events. The value of exercise testing in assessing myocardial ischemia to date has been limited because of resting ECG and wall motion abnormalities. We recognize that new or worsened ST- or T-wave changes with

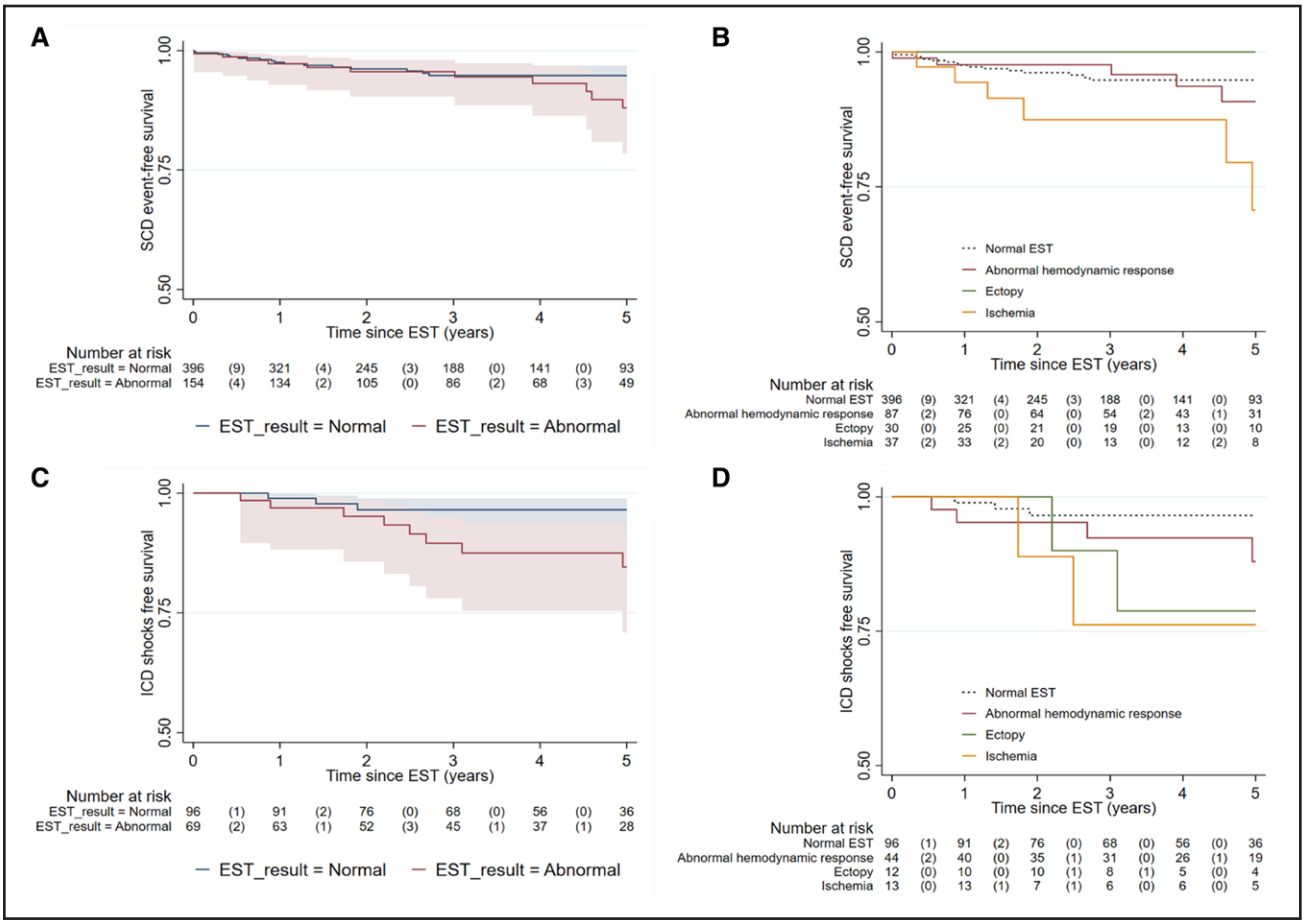

Figure 2. Sudden cardiac death or aborted sudden cardiac arrest.
A, Kaplan-Meier analysis showed no difference in 5-year freedom from sudden cardiac death (SCD) or aborted sudden cardiac arrest (SCA) between patients with normal exercise stress test (EST) results (n=396; blue) and those with abnormal exercise test results (n=154; red; 95% vs 88%; *P*=0.220). **B**, Kaplan-Meier analysis showed a difference in SCD event-free survival by type of exercise-induced abnormality (*P*=0.007). Compared with those with normal exercise testing results (dashed black), 5-year SCD event-free survival was lower for those with exercise-induced ischemia (orange; 71%; hazard ratio, 4.02 [95% CI, 1.57–10.28]; *P*=0.004). Five-year SCD event-free survival for those with abnormal blood pressure response (red; 91%) was not different from those with normal exercise test results. There were no SCD events in the exercise-induced ectopy-only subgroup (green). **C**, In the subset of patients with primary prevention implantable cardioverter defibrillator (ICD) implantation after an exercise test (n=165), 5-year freedom from appropriate ICD discharges was lower for those with abnormal exercise test results (n=69; red) compared with those with normal exercise test results (n=96; blue; 85% vs 97%, respectively; *P*=0.032; hazard ratio, 3.86 [95% CI, 1.02–14.5]). **D**, Kaplan-Meier analysis showed no significant difference in appropriate ICD discharges by type of exercise-induced abnormality (*P*=0.0951). Compared with those with a normal exercise test result, 5-year event-free survival was 76% in those with exercise-induced ischemia (orange; hazard ratio, 5.83 [95% CI, 0.97–35.0]; *P*=0.054), 79% in those with ectopy (green; hazard ratio, 5.7 [95% CI, 0.95–34.1]; *P*=0.056), and 88% in those with abnormal blood pressure response (red; hazard ratio, 1.39 [95% CI, 0.64–12.94]; *P*=0.164).

exercise do not provide a mechanism for ischemia, and may not always be driven purely by an ischemic process. However, our findings suggest that ST- or T-wave changes during exercise are important to consider in risk stratification in childhood HCM. The independent association of exercise test abnormalities with transplant-free survival (and of exercise-induced ischemia with SCD) emphasizes the importance of routine exercise testing as part of ongoing surveillance and risk assessment for SCD as well as progression to advanced heart failure.

Besides an abnormal exercise test result, a higher LVPWD *z* score was independently associated with lower transplant-free survival. This has not been reported previously. Other studies have reported an association of LVPWD with SCD and with survival after septal reduction therapy.[1,9,10] The mechanism for adverse outcomes in patients with high LVPWD scores is not known. Whether this reflects a genetically driven high-risk phenotype requires further study.

As described earlier, an important finding was that the types of exercise abnormalities confer different risks, suggesting that these abnormalities are manifestations of different pathophysiologic drivers. Whereas a blunted BP response is usually linked to LVOTO or diastolic dysfunction, myocardial ischemia is multifactorial. There are many factors that can lead to myocardial ischemia, including myocardial hypertrophy, impaired coronary flow reserve, microvascular dysfunction, and myocardial bridging.[11–14] The resulting ischemia can be exacerbated by

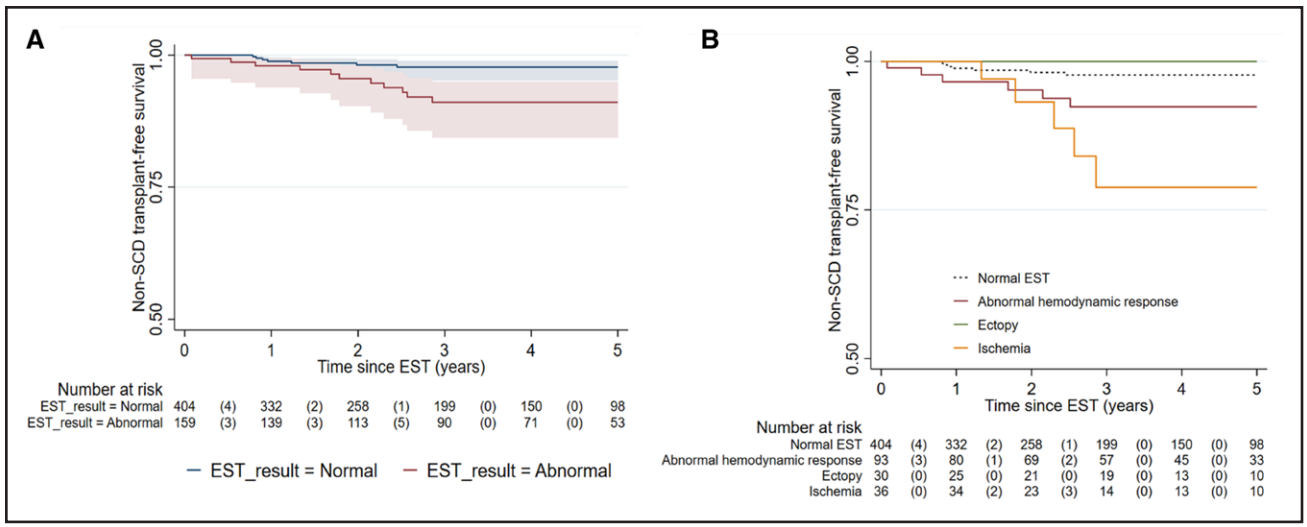

Figure 3. Other deaths or transplant.

A, Kaplan-Meier analysis showed that compared with those with normal exercise stress test (EST) results (n=406; blue), 5-year freedom from other deaths or transplant was lower in the abnormal exercise test results group (n=159; red; 98% vs 91%; *P*=0.004 by log-rank test). **B**, Kaplan-Meier analysis showed a difference in outcome by type of exercise-induced abnormality (*P*=0.004). Compared with those with normal exercise test results (dashed black), 5-year freedom from other deaths or transplant was lower for those with exercise-induced ischemia (orange; 79%; hazard ratio, 7.64 [95% CI, 2.42–24.08]; *P*=0.001) and for those with an abnormal blood pressure response (red; 92%; hazard ratio, 3.33 [95% CI, 1.12–9.91]; *P*=0.031). There were no deaths or heart transplants in the exercise-induced ectopy-only subgroup (green). SCD indicates sudden cardiac death.

high myocardial oxygen demand caused by myocardial hypercontractility, increased muscle mass, and increased LV myocardial stress caused by elevated left-sided filling pressures. Myocardial perfusion mismatch can contribute to myocyte dysfunction, myocyte loss, and myocardial fibrosis, which, together, can manifest as systolic or diastolic dysfunction.[15–18] It is notable that only 2% of our cohort had systolic dysfunction (ie, LV ejection fraction <50%), but a much higher proportion (16/407 [4%]) died of heart failure or underwent transplant. This suggests that diastolic heart failure may have been a contributor to these events.

Myocardial ischemia may also predispose to life-threatening arrhythmias.[15–18] In this context, it is noteworthy that a higher proportion of patients in our cohort with an abnormal exercise test result had not only more SCD events but also more appropriate ICD shocks after ICD insertion, which suggests greater arrhythmogenicity in this subgroup. We deliberately excluded ICD shocks as an SCD event in the primary analysis because ICDs were more frequent in those with an abnormal exercise test result. Nonetheless, on subgroup analysis of patients with primary prevention ICD, we found lower freedom from appropriate shocks for those with an abnormal exercise test result. Although further studies are needed to fully incorporate exercise test abnormalities in risk prediction models for SCD, the findings signal the potential additive value of exercise test results in identifying highest-risk patients who may benefit from an ICD.

Exercise-induced ventricular ectopy alone was not associated with either SCD or transplant-free survival. We did not examine the association of an isolated blunted heart rate response because a substantial proportion of patients (39%) were on a beta-blocker at the time of the exercise test, which can interfere with the normal chronotropic response to exercise.

Whereas this study found associations between exercise measures and outcomes in children with HCM, clinical practice varies across institutions, with some institutions offering routine exercise testing to all patients with HCM old enough to exercise and others performing exercise testing only for selected patients. However, we found few differences between the children who underwent exercise testing and those who did not, with the exception of lower frequencies of myectomy and aborted SCA, and a higher frequency of nonsustained ventricular tachycardia on Holter monitor in those who underwent exercise testing. On the basis of the limited variables compared, this suggests that there may not have been a significant bias toward exercise testing in higher-risk patients or that patients who underwent exercise testing had independent risk factors for higher mortality.

Limitations

Our study has some limitations inherent in a retrospective study, including the potential for a selection bias and the confounding effects of practice variability. However, as outlined earlier, we did not find substantial practice variability, nor did we encounter a selection bias toward exercise testing in higher-risk patients. There was variability in the type of exercise testing used at different sites, but

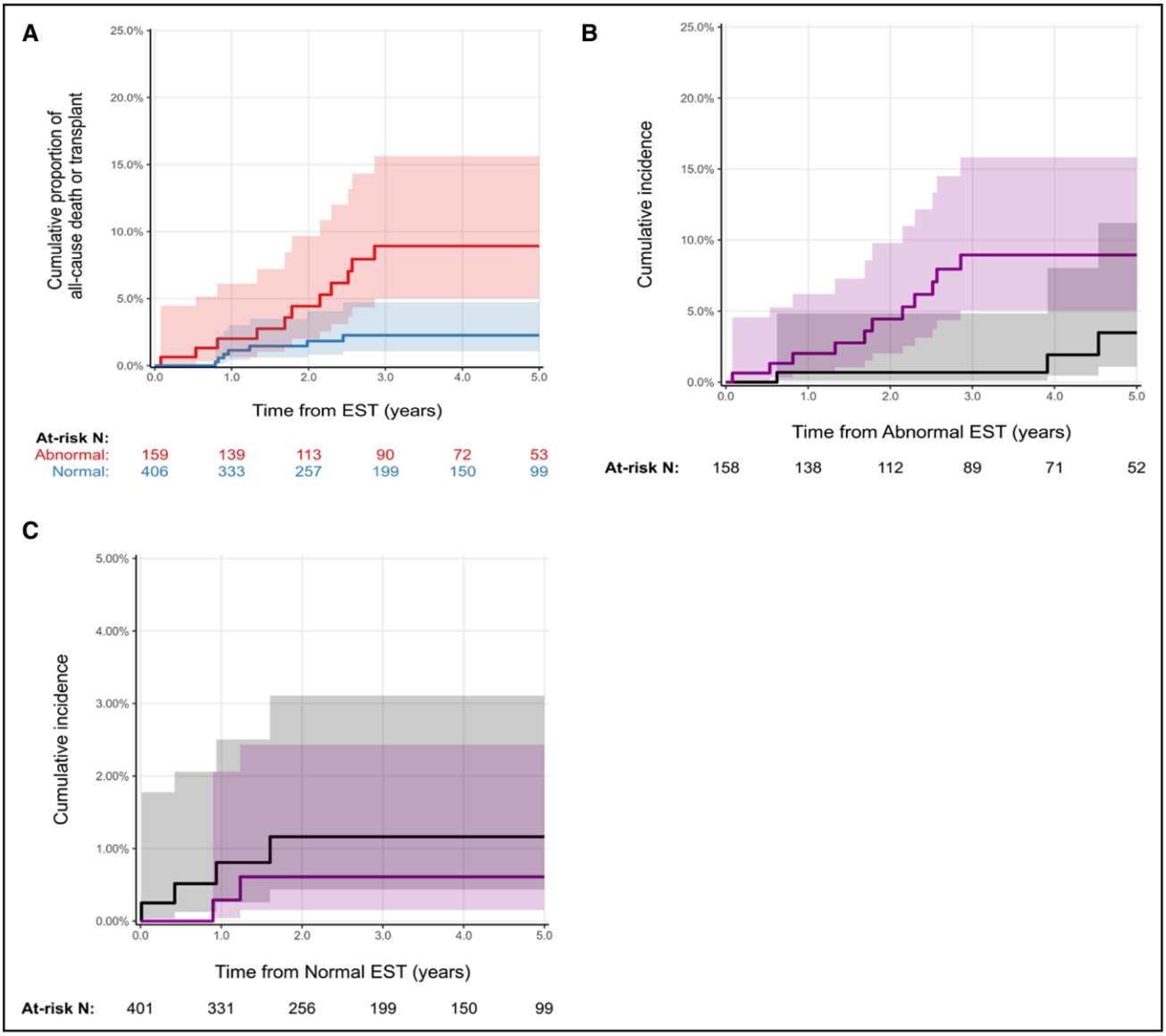

Figure 4. Competing outcomes of sudden cardiac death vs other deaths or transplant.
A, The 5-year cumulative proportion of death or transplant from the time of the exercise stress test (EST) was significantly higher among patients with an abnormal test result (red) compared with those with normal test results (blue; 8.9% vs 2.3%; log-rank *P*=0.004). **B**, Competing outcomes analysis showing the 5-year cumulative incidence of sudden cardiac death (SCD; black) and other deaths or transplant (purple) for patients with an abnormal exercise test result. **C**, Competing outcomes analysis showing the 5-year cumulative incidence of SCD (black) and other deaths or transplant (purple) for patients with a normal exercise test result. The 5-year cumulative incidence of SCD was not different between those with abnormal vs normal exercise test results (3.4% vs 1.1%, respectively; Gray test *P*=0.48). The 5-year cumulative incidence of other causes of death or transplant was higher for those with an abnormal vs normal test results (8.9% vs 0.6%, respectively; Gray test *P*=0.004).

regardless of treadmill or bicycle use, all tests were performed in clinical exercise laboratories with standardized protocols and standardized interpretation. The multivariable risk predictor analysis for transplant-free survival was limited by having to exclude patients with missing echocardiographic data; in addition, race and ethnicity could not be analyzed as predictors because these data were missing in >50% of cases. Because CPET was not performed routinely at all institutions, we were unable to assess the association of peak Vo_2 and other ventilatory measures with clinical outcomes.

CONCLUSIONS

The relatively high prevalence of exercise test abnormalities in our study suggests that exercise testing should be performed as part of ongoing surveillance for risk assessment in children with HCM. The type of response to exercise provides prognostic information on the 5-year risk of all-cause death or transplant and SCD. An ischemic response to exercise is a particularly concerning finding given its strong association with adverse clinical outcomes. Risk prediction models for adverse cardiac

outcomes in children with HCM should incorporate exercise test results.

ARTICLE INFORMATION

Received October 7, 2022; accepted November 3, 2022.

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Sources of Funding

This project was supported through funding from the Ted Rogers Centre for Heart Research, the Heart and Stroke Foundation of Canada/Robert M Freedom Chair, and the Canadian Institutes of Health Research to Dr Mital.

Disclosures

Dr Mital is a consultant for Bristol Myers Squibb and Tenaya Therapeutics and has received unrestricted education funding from Bristol Myers Squibb. Dr Conway is a medical monitor for the Pumpkin Trial and has received unrestricted education funding from Abbott. Dr Aziz is on the medical advisory board for Medtronic. Dr Balaji is a consultant for Milestone Pharmaceuticals and Janssen Pharmaceuticals, and is a recipient of a research support grant from the Medtronic External Research program. Dr Godown is a consultant for Daiichi-Sankyo. Dr Jeewa is a medical monitor for the Pumpkin Trial and consultant for Abbott and Ultragenyx. Dr Kantor is a consultant for Novartis and AstraZeneca. Dr Rossano is a consultant for Merck, Bayer, MyoKardia, and Cytokinetics. The remaining authors have nothing to disclose.

Supplemental Material

Tables S1 and S2

Figure S1

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