Original research

Factors associated with high-intensity physical activity and sudden cardiac death in hypertrophic cardiomyopathy

Hyun-Jung Lee , Seo-Yeon Gwak , Kyu Kim, Iksung Cho, Chi Young Shim , Jong-Won Ha , Geu-Ru Hong

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/heartjnl-2024-324928).

Yonsei University College of Medicine, Seoul, The Republic of Korea

Correspondence to
Dr Geu-Ru Hong;
GRHONG@yuhs.ac

Received 17 August 2024
Accepted 29 November 2024
Published Online First
23 January 2025

To cite: Lee H-J, Gwak S-Y, Kim K, *et al*. *Heart* 2025;**111**:253–261.

ABSTRACT

Background High-intensity physical activity has traditionally been discouraged in patients with hypertrophic cardiomyopathy due to concerns about triggering sudden cardiac death. However, current guidelines adopt a more liberal stance, and evidence on risk factors for exercise-related sudden cardiac death remains limited. This study investigated the clinical, morphological and genetic factors associated with high-intensity physical activity-related sudden cardiac death in hypertrophic cardiomyopathy.

Methods This retrospective study included 75 patients with documented sudden cardiac death events from a cohort of 2619 patients with hypertrophic cardiomyopathy evaluated between 2005 and 2023. Physical activity levels at the time of the sudden cardiac death event were classified as high-intensity (≥6 metabolic equivalents) or low-intensity to moderate-intensity. Clinical and imaging characteristics, cardiopulmonary exercise test findings and genetic data were compared between the groups.

Results Among the 75 patients, 15 (20%) experienced sudden cardiac death events during high-intensity activity. These patients were younger than those with events during low-intensity or moderate-intensity activity (median age: 25 (IQR 16–43) years vs 56 (48–64) years, p<0.001). High-intensity activity-related events were associated with higher European Society of Cardiology sudden cardiac death risk scores (median 4.9 vs 2.4, p=0.023) and fewer ventricular arrhythmias during exercise testing. However, there were no differences in the degree of left ventricular hypertrophy, left ventricular outflow tract obstruction, left ventricular systolic or diastolic function or genetic findings between groups. In multivariable analysis, younger age was the only independent risk factor of high-intensity activity-related sudden cardiac death events. Recurrent events in patients who survived initial high-intensity activity-related sudden cardiac death were triggered by subsequent high-intensity activity.

Conclusions High-intensity physical activity-related sudden cardiac death in hypertrophic cardiomyopathy is associated with younger age; however, in this small cohort, no associations were found with traditional risk factors, including left ventricular hypertrophy or obstructive physiology.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Exercise restrictions for hypertrophic cardiomyopathy have evolved, but concerns about high-intensity activity triggering sudden cardiac death persist.

⇒ Sudden cardiac death risk stratification traditionally focuses on morphological and functional cardiac abnormalities, but its utility for exercise-related events remains unclear.

WHAT THIS STUDY ADDS

⇒ Younger patients were at greater risk for sudden cardiac death during high-intensity physical activity, while conventional risk factors, such as left ventricular hypertrophy and outflow tract obstruction, were not associated with activity-related events.

⇒ Recurrent events in survivors of high-intensity activity-related sudden cardiac death were linked to subsequent high-intensity activity, highlighting a potential trigger mechanism.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Exercise restrictions in hypertrophic cardiomyopathy should consider patient age and previous events rather than relying solely on conventional risk factors.

⇒ Future research should refine risk stratification tools and develop age-specific exercise guidelines for patients with hypertrophic cardiomyopathy.

INTRODUCTION

Exercise significantly increases cardiac load through elevated cardiac output, heart rate, myocardial contractility, circulating catecholamines, core temperature, electrolyte shifts and acid-base disturbance, potentially triggering fatal arrhythmias and sudden cardiac death (SCD) when superimposed on the pathological cardiac substrate.[1] Historically, exercise restrictions were recommended for all patients with hypertrophic cardiomyopathy (HCM), leading many to reduce physical activity (PA) after diagnosis.[2 3] However, sedentary lifestyles can result in obesity and increased atherosclerotic cardiovascular risk, worsening prognosis. Obesity is prevalent in patients with HCM and associated with

Table 1 Differences in clinical, morphological and genetic characteristics between patients with and without SCD events

	Patients without SCD (n=2538)	Patients with SCD (n=81)	P value
Age at index evaluation, years	61 (51–70)	50 (42–60)	<0.001
Age at SCD event, years		54 (41.5–62.5)	
Male	1656 (65.2%)	62 (76.5%)	0.047
Comorbidities			
Baseline atrial fibrillation	457 (18.0%)	23 (28.4%)	0.026
Coronary artery disease	492 (19.4%)	15 (18.5%)	0.959
Previous HF hospitalisation	57 (2.2%)	3 (3.7%)	0.627
Prior stroke	236 (9.3%)	5 (6.2%)	0.446
Hypertension	1507 (59.4%)	37 (45.7%)	0.019
Diabetes	398 (15.7%)	9 (11.1%)	0.336
End-stage renal disease	43 (1.7%)	1 (1.2%)	0.999
COPD	37 (1.5%)	1 (1.2%)	0.999
Cancer	256 (10.1%)	4 (4.9%)	0.181
Echocardiography			
Obstructive HCM	434 (17.1%)	20 (24.7%)	0.104
Pure apical HCM	427 (16.8%)	6 (7.4%)	0.036
LV apical aneurysm	84 (3.3%)	7 (8.6%)	0.023
Maximum LVWT, mm	18 (16–20)	20 (19–23)	<0.001
LVEDD, mm	48 (44–51)	48 (43.5–53)	0.377
LVESD, mm	30 (27–33)	31 (27–36)	0.058
LVEF, %	70 (65–74)	66 (54–74)	0.001
E/A ≥2	101 (4.6%)	11 (15.9%)	<0.001
Medial e', cm	4.5 (3.8–5.9)	4.0 (3.0–5.0)	0.002
E/e'	13.5 (10.4–18.0)	15.1 (11.0–20.0)	0.004
RVSP, mm Hg	27 (23–33)	31 (26–39)	<0.001
SCD risk			
AHA/ACC risk factors*			
Family history of SCD	157 (6.2)	13 (16.0)	0.001
History of syncope	131 (5.2)	16 (19.8)	<0.001
Maximum LVWT ≥30 mm	38 (1.5)	6 (7.4)	<0.001
LVEF <50%	76 (3.0%)	18 (22.2%)	<0.001
LV apical aneurysm	84 (3.3%)	7 (8.6%)	0.023
NSVT on Holter (n=1644)	123 (7.8%)	14 (24.1)	<0.001
Number of AHA/ACC risk factors	0 (0–0)	1 (0–2)	<0.001
Positive AHA/ACC risk factor	488 (19.2%)	51 (63.0%)	<0.001
Positive major AHA/ACC risk factor	412 (16.2%)	45 (55.6%)	<0.001
ESC SCD risk score, %	1.5 (1.1–2.1)	2.5 (1.8–4.9)	<0.001
ESC SCD risk group			<0.001
Low risk (<4%)	2400 (94.6%)	54 (66.7%)	
Intermediate risk (4%~6%)	94 (3.7%)	13 (16.0%)	
High risk (≥6%)	44 (1.7%)	14 (17.3%)	
Genetic testing results (n=431)			0.021
None/Benign/Likely benign	199 (49.6%)	7 (23.3%)	
Variant of unknown significance	38 (9.5%)	4 (13.3%)	
Pathogenic/Likely pathogenic	164 (40.9%)	19 (63.3%)	

*Assessment of extensive LGE on CMR was not available for the whole HCM population.
AHA/ACC, American Heart Association/American College of Cardiology; CMR, cardiovascular magnetic resonance; COPD, chronic obstructive pulmonary disease; ESC, European Society of Cardiology; HCM, hypertrophic cardiomyopathy; HF, heart failure; LGE, late gadolinium enhancement; LV, left ventricular; LVEDD, LV end-diastolic dimension; LVEF, LV ejection fraction; LVESD, LV end-systolic dimension; LVWT, LV wall thickness; METs, metabolic equivalents; NSVT, non-sustained ventricular tachycardia; PA, physical activity; RVSP, right ventricular systolic pressure; SCD, sudden cardiac death.

greater phenotypical expression including greater left ventricular (LV) mass, more obstructive physiology, worse symptoms and more heart failure and atrial fibrillation.[4 5] Recent evidence suggests benefits of exercise outweigh risks in most patients with HCM.[6–8] Current guidelines adopt a more liberal approach to exercise restriction, and recommend low-intensity to moderate-intensity PA, no longer universally banning high-intensity PA in patients with HCM.[1 9 10] However, recommendations on high-intensity PA including competitive sports diverge in the European and American guidelines, and the safety of high-intensity PA in all patients with HCM remains uncertain, although recent studies suggest it does not worsen outcomes.[7 8 11 12] Furthermore, evidence is lacking on whether conventional SCD risk stratification or morphological expression should determine eligibility for high-intensity PA. This study investigates PA level at the time of the SCD event and its association with clinical and morphological characteristics, SCD risk profile and genetics in patients with HCM with SCD events, aiming to identify factors associated with high-intensity exercise-related SCD.

METHODS

Study population

This retrospective study analysed consecutive patients with HCM evaluated between January 2005 and April 2023 at a high-volume tertiary centre (Severance Hospital, Korea). HCM was diagnosed by maximal end-diastolic LV wall thickness ≥15 mm (≥13 mm in patients with family history of HCM or pathogenic sarcomeric gene variants) in the absence of other cardiac, systemic or metabolic diseases capable of causing the magnitude of hypertrophy.[9] Patients with SCD events and documented PA at the time of the SCD event were included. In patients with multiple SCD events, the first documented event was used for the main analysis.

Patient and public involvement

Patients/Public were not involved in the design, conduct, reporting or dissemination plans of this research.

Data collection and SCD risk stratification

Details are available in online supplemental methods. Data on comorbidities and outcomes until September 2023 were collected from medical records, and mortality and causes of death were confirmed from the National Death Registration Records of Korea. Holter monitoring, cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE) imaging, cardiopulmonary exercise testing (CPET) and genetic testing were performed at the attending physician's discretion. Genetic testing identified sarcomeric gene variants definitively associated with HCM, classified as pathogenic, likely pathogenic, variant of unknown significance or none/benign/likely benign according to current criteria.[13] Thick filament variants included myosin and myosin-binding protein genes, and thin filament variants included actin, troponin and tropomyosin genes.[14]

SCD risk stratification was performed according to the 2024 American Heart Association/American College of Cardiology (AHA/ACC) and 2014 European Society of Cardiology (ESC) HCM guidelines,[10 15] also validated in Asian patients.[16] Patients with one or more major AHA/ACC risk factors or an ESC 5-year SCD risk score of ≥6 had class IIa recommendation for primary SCD prevention with implantable cardioverter-defibrillators (ICD) and were considered high-risk.

Definition of SCD events

SCD events included SCD, aborted SCD and appropriate ICD shock. SCD was defined as sudden death presumed to be of

Table 2 Clinical and morphological characteristics according to PA level during the SCD event

	Total (n=75)	Group 1 high-intensity PA (–) (n=60)	Group 2 high-intensity PA (+) (n=15)	P value
PA level at time of event (METs)	1.5 (1.0–4.2)	1.3 (1.0–2.5)	7.5 (6.4–10.5)	<0.001
Age at SCD event, years	54 (41.5–62.5)	56 (47.5–64.5)	25 (16.5–42.5)	<0.001
<40	18 (24.0%)	9 (15.0%)	9 (60%)	<0.001
40–59	33 (44.0%)	27 (45.0%)	6 (40%)	
≥60	24 (32.0%)	24 (40.0%)	0 (0%)	
Male	60 (80.0%)	50 (83.3%)	10 (66.7%)	0.279
Type of SCD event				0.001
SCD	11 (14.7%)	11 (18.3%)	0 (0%)	
Aborted SCD	43 (57.3%)	28 (46.7%)	15 (100%)	
Appropriate ICD shock	21 (28.0%)	21 (35.0%)	0 (0%)	
Comorbidities				
Baseline atrial fibrillation	21 (28.0%)	19 (31.7%)	2 (13.3%)	0.274
Coronary artery disease	13 (17.3%)	12 (20.0%)	1 (6.7%)	0.402
Previous HF hospitalisation	3 (4.0%)	3 (5.0%)	0 (0%)	0.883
Prior stroke	5 (6.7%)	5 (8.3%)	0 (0%)	0.563
Hypertension	32 (42.7%)	28 (46.7%)	4 (26.7%)	0.267
Diabetes	8 (10.7%)	7 (11.7%)	1 (6.7%)	0.925
End-stage renal disease	1 (1.3%)	1 (1.7%)	0 (0%)	0.999
COPD	1 (1.3%)	1 (1.7%)	0 (0%)	0.999
Cancer	3 (4.0%)	3 (5.0%)	0 (0%)	0.883
Echocardiography				
Obstructive HCM	19 (25.3%)	14 (23.3%)	5 (33.3%)	0.642
Pure apical HCM	4 (5.3%)	4 (6.7%)	0 (0%)	0.700
LV apical aneurysm	7 (9.3%)	6 (10.0%)	1 (6.7%)	0.999
Maximum LVWT, mm	21 (19–23)	20 (19–23)	21 (19.5–24)	0.406
LVEDD, mm	47.5 (43–52)	50 (44.5–53)	43 (41–46.5)	0.004
Indexed LVEDD, mm/m^2	26.0 (24.5–28.4)	26.6 (24.6–28.3)	25.3 (23.6–28.2)	0.270
LVESD, mm	31 (26–37)	32 (27.5–36.5)	29 (25–30)	0.017
Indexed LVESD, mm/m^2	17.1 (15.1–20.1)	17.7 (15.5–20.4)	16.0 (14.9–17.1)	0.154
LVEF, %	66 (56–72)	65 (49–73)	69 (65.5–71)	0.164
E/A ≥2	11 (17.2%)	8 (16.3%)	3 (20.0%)	0.999
Medial e', cm	4.0 (3.0–5.0)	4.0 (3.0–5.0)	4.0 (3.8–5.0)	0.369
E/e'	15.0 (11.0–20.0)	15.0 (11.5–21.0)	15.0 (10.9–17.5)	0.536
RVSP, mm Hg	31 (26–37)	32 (25.5–40.5)	28 (27–36)	0.588

COPD, chronic obstructive pulmonary disease; HCM, hypertrophic cardiomyopathy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVEF, LV ejection fraction; LVEDD, LV end-diastolic dimension; LVESD, LV end-systolic dimension; LVWT, LV wall thickness; METs, metabolic equivalents; PA, physical activity; RVSP, right ventricular systolic pressure; SCD, sudden cardiac death.

cardiac cause occurring within 1 hour of symptom onset or within 24 hours of last being seen alive.[17] Patients with ICD underwent interrogation regularly, and appropriate ICD shocks were defined as shocks discharged to treat sustained ventricular tachycardia or fibrillation, excluding antitachycardia pacing.[17]

Definition of PA level

Descriptions of PA at the time of SCD events were collected from medical records, which were documented by the medical staff from patient or family interviews during emergency room or hospital visits after the SCD events. Patients were grouped by PA level at SCD event: group 2 included high-intensity exercise-related SCD events, defined as happening during or immediately after high-intensity exercise or PA, while group 1 included SCD events happening at rest or during light or moderate PA. PA level at the SCD event were categorised as low-intensity (<3 metabolic equivalents (METs), moderate-intensity (≥3 to <6 METs) and high-intensity (≥6 METs) activity,[1 9 18] with the METs level of each activity approximated by the 2024 Adult Compendium of Physical Activities.[18] Examples of low-intensity PA included sitting, standing, eating, riding in a car and walking at a slow pace (<4 km/hour), for example, walking from car to house or worksite or to an outhouse. Moderate-intensity PA included walking at a moderate or brisk pace (4–7 km/hour), general garden work with moderate effort, commercial fishing with moderate effort, and sports such as golf. High-intensity PA included jog/walk combination, running (≥6.5 km/hour), climbing stairs at a normal or fast pace, and sports such as soccer, basketball, badminton or swimming.

Statistical analysis

Cross-sectional analysis using data at the timepoint of the SCD event was performed to identify factors associated with high-intensity PA-related SCD events. Patient characteristics were compared between groups using the Student's t-test, Mann-Whitney U test, one-way analysis of variance, Kruskal-Wallis test, χ^2 test or Fisher's exact test, as appropriate. Continuous data are presented as mean±SD or median (IQR) depending on the normality of distribution, and categorical data, as number (%). Logistic regression was performed to identify variables

Table 3 SCD risk profile according to PA level during the SCD event

	Total (n=75)	Group 1 high-intensity PA (–) (n=60)	Group 2 high-intensity PA (+) (n=15)	P value
AHA/ACC risk factors				
Family history of SCD	12 (16.0)	11 (18.3)	1 (6.7%)	0.429
History of syncope	16 (21.3)	10 (16.7)	6 (40.0%)	0.105
Max. LVWT ≥30 mm	6 (8.0)	5 (8.3)	1 (6.7%)	0.999
LVEF <50%	17 (22.7%)	16 (26.7%)	1 (6.7%)	0.190
LV apical aneurysm	7 (9.3%)	6 (10.0%)	1 (6.7%)	0.999
NSVT on Holter (n=53)	13 (24.5%)	10 (22.7%)	3 (33.3%)	0.804
Extensive LGE on CMR (n=33)	14 (42.4%)	14 (53.8%)	0 (0%)	0.033
Number of AHA/ACC risk factors	1 (0–2)	1 (0–2)	1 (0–1)	0.325
Positive AHA/ACC risk factor	49 (65.3%)	40 (66.7%)	9 (60%)	0.856
Positive major AHA/ACC risk factor	44 (58.7%)	36 (60.0%)	8 (53.3%)	0.860
ESC SCD risk score, %	2.6 (1.9–5.0)	2.4 (1.7–4.6)	4.9 (2.5–7.3)	0.023
ESC SCD risk group				0.133
Low risk (<4%)	51 (68.0%)	44 (73.3%)	7 (46.7%)	
Intermediate risk (4%~6%)	10 (13.3%)	7 (11.7%)	3 (20%)	
High risk (≥6%)	14 (18.7%)	9 (15.0%)	5 (33.3%)	

AHA/ACC, American Heart Association/American College of Cardiology; CMR, cardiovascular magnetic resonance; ESC, European Society of Cardiology; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, LV ejection fraction; LVWT, LV wall thickness; NSVT, non-sustained ventricular tachycardia; PA, physical activity; SCD, sudden cardiac death.

associated with high-intensity PA-related SCD events and the degree of association expressed as ORs with 95% CIs. Variables with p values of <0.100 on univariable analysis were included in the multivariable models. Two-sided p values <0.05 were considered significant. Relationships between significant variables and risk for high-intensity PA-related SCD events were plotted using restricted cubic splines. Analyses were conducted using R V.4.3.2 (The R Project for Statistical Computing, Austria).

RESULTS

Study population

Among 2619 consecutive patients with HCM, SCD events occurred in 81 (3.1%). Differences in the clinical, morphological and genetic characteristics between patients with and without SCD events are presented in table 1. Overall, patients with SCD events had a higher SCD risk profile, were younger, had more atrial fibrillation, less apical HCM, more LV apical aneurysms, greater LV wall thickness, lower LV ejection fraction, greater LV diastolic dysfunction and a higher prevalence of pathogenic variants.

PA level at the SCD event was documented for 75 patients, who were included in the study. Details on the PA and estimated METs level during the SCD events are presented in online supplemental data. The 75 SCD events included 11 SCD, 43 aborted SCD and 21 appropriate ICD shocks. Median age at SCD event was 54 (IQR 41.5–62.5) years and 60 (80.0%) were men (table 2). Approximately one-fourth (25.3%) had obstructive HCM (maximum LV outflow tract (LVOT) pressure gradient ≥30 mm Hg), and four (5.3%) had pure apical HCM. LV apical aneurysm was present in seven patients (9.3%). Thirty-three patients underwent CMR, and extensive LGE was present in 14 (42.4%). Half of the patients had a major AHA risk factor

Table 4 Sarcomeric variants according to PA level during the SCD event

	Total (n=29)	Group 1 high-intensity PA (–) (n=22)	Group 2 high-intensity PA (+) (n=7)	P value
Genetic testing results				0.353
None/Benign/Likely benign	7 (24.1%)	5 (22.7%)	2 (28.6%)	
Variant of unknown significance	4 (13.8%)	2 (9.1%)	2 (28.6%)	
Pathogenic/Likely pathogenic	18 (62.1%)	15 (68.2%)	3 (42.9%)	
Pathogenic/Likely pathogenic variants (n=18)				
Thick filament variants*	11 (61.1%)	10 (66.7%)	1 (33.3%)	0.665
Thin filament variants†	7 (38.9%)	5 (33.3%)	2 (66.7%)	
Specifics of pathogenic/likely pathogenic variants (n=18)				
MYBPC3, MYL2	1 (5.6%)	0 (0%)	1 (33.3%)	
MYBPC3	7 (38.9%)	7 (46.7%)	0 (0%)	
MYH7	3 (16.7%)	3 (20.0%)	0 (0%)	
TNNI3	4 (22.2%)	4 (26.7%)	0 (0%)	
TNNC1	1 (5.6%)	1 (6.7%)	0 (0%)	
TNNT2	1 (5.6%)	0 (0%)	1 (33.3%)	
TPM1	1 (5.6%)	0 (0%)	1 (33.3%)	

*Including those related to myosin and myosin-binding protein.
†Including those related to actin, troponin and tropomyosin.
PA, physical activity; SCD, sudden cardiac death.

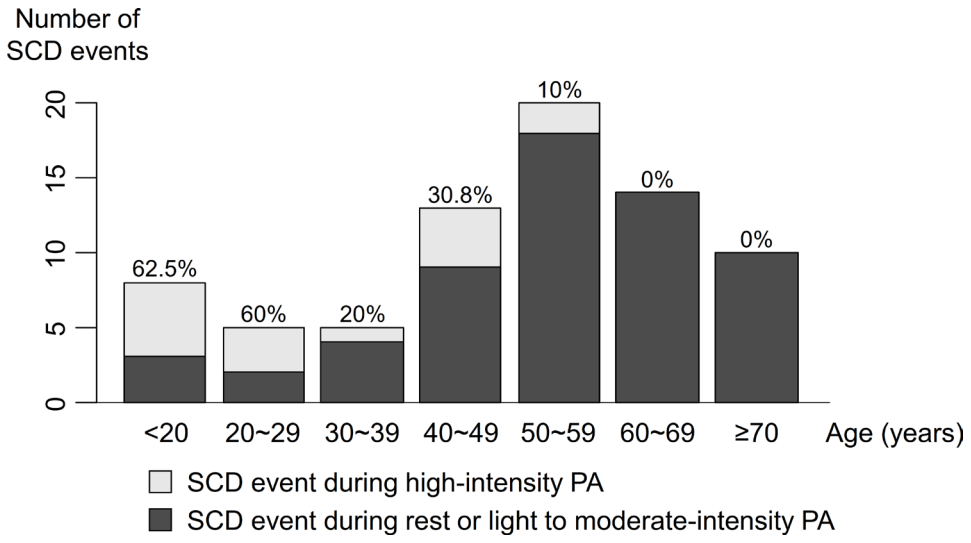

Figure 1 Proportion of high-intensity PA-related SCD events according to age. The number above the bar plots indicate the proportion of high-intensity PA-related SCD events. PA, physical activity; SCD, sudden cardiac death.

(n=44, 58.7%) (table 3). Median ESC SCD risk score was 2.6 (IQR 1.9–5.0), with only 14 (18.7%) patients in the high-risk category. Twenty-nine patients underwent genetic testing, and 18 (62.1%) were found to have pathogenic/likely pathogenic variants (table 4).

Comparison of clinical and morphological characteristics

There were 60 patients (80%) in group 1 (low-intensity/moderate-intensity PA) and 15 patients (20%) in group 2 (high-intensity PA). The median PA level was 1.3 (IQR 1.0–2.5) METs for group 1 and 7.5 (6.4–10.5) METs for group 2. Group 2 patients were markedly younger than group 1 patients (56 (47–65) vs 25 (16.5–42.5) years, p<0.001) (table 2). All patients in group 2 were aged <60 years, while 40% of group 1 were aged ≥60 years. The proportion of high-intensity PA-related SCD events significantly decreased with age (p-for-trend <0.001) (figure 1). All group 2 patients presented as aborted SCD. No significant differences in comorbidities were noted between groups. Absolute LV dimensions were smaller in group 2, but were not significantly different after indexing for body surface area. No significant differences were observed in obstructive physiology, pure apical HCM, apical aneurysm, maximal LV wall thickness and parameters of LV systolic and diastolic function between groups.

Comparison of SCD risk profile

No significant differences were found in the number of AHA/ACC SCD risk factors between groups (table 3). The proportion of patients with ≥1 major SCD risk factors did not differ significantly (60.0% vs 53.3%, p=0.860). The prevalence of SCD risk factors did not differ significantly between groups, except for the presence of extensive LGE. CMR was performed in 26 of group 1 patients (43.3%) and seven of group 2 patients (46.7%); extensive LGE was present in half of group 1 patients (53.8%) and none of group 2 patients. Group 2 had higher ESC SCD risk scores than group 1 (2.4 (IQR 1.7–4.6) vs 4.9 (2.5–7.3), p=0.023), but the proportion of high-risk category did not differ significantly (15.0% vs 33.3%, p=0.133).

Comparison of pathogenic sarcomeric variants

There was no difference in the proportion of patients with pathogenic/likely pathogenic sarcomeric variants between groups 1 and 2 (68.2% vs 42.9%, p=0.353) (table 4). Thick or thin filament variants also did not differ significantly between groups.

Comparison of CPET

Thirty-five patients underwent CPET (26 in group 1; 9 in group 2), and there were no significant differences in most parameters

Table 5 Cardiopulmonary exercise testing results according to PA level during the SCD event

	Total (n=35)	Group 1 high-intensity PA (–) (n=26)	Group 2 high-intensity PA (+) (n=9)	P value
Maximum workload (estimated METs)	8.9±2.4	8.6±2.6	9.8±1.8	0.255
Peak oxygen consumption (peak VO_2), mL/kg/min	21.8±6.9	20.8±7.0	24.8±6.2	0.137
Aerobic capacity, % predicted	60.6±19.2	62.0±20.8	56.6±14.1	0.469
Respiratory exchange ratio	1.1±0.1	1.1±0.1	1.1±0.1	0.557
Ventilatory efficiency (V_E/VCO_2 slope)	33.0 (29.5–38.2)	34.5 (29.6–40.6)	31.3 (26.6–33.0)	0.089
ST depression (>2 mm)	10 (28.6%)	7 (26.9%)	3 (33.3%)	0.999
Ventricular arrhythmia				0.041
None	12 (34.3%)	6 (23.1%)	6 (66.7%)	
Ventricular premature beats	20 (57.1%)	18 (69.2%)	2 (22.2%)	
Non-sustained ventricular tachycardia	3 (8.6%)	2 (7.7%)	1 (11.1%)	

MET, metabolic equivalent; PA, physical activity; SCD, sudden cardiac death.

Table 6 Risk factors of high-intensity exercise-related SCD events: logistic regression

	OR (95% CI)	P value
Univariable analysis		
Age at SCD event, per 1 year	0.92 (0.88 to 0.96)	<0.001
Male sex	0.40 (0.11 to 1.42)	0.157
Maximum LV wall thickness, per 1 mm	1.04 (0.92 to 1.17)	0.541
Obstructive physiology	1.64 (0.48 to 5.61)	0.429
Maximum LVOT gradient, per 10 mm Hg	1.06 (0.90 to 1.24)	0.474
ESC SCD risk score, per 1%	1.26 (1.03 to 1.55)	0.023
ESC SCD risk group (ref. low-risk group)		
Intermediate-risk group	2.69 (0.56 to 13.0)	0.216
High-risk group	3.49 (0.90 to 13.5)	0.070
Positive AHA/ACC major risk factor	0.76 (0.24 to 2.38)	0.640
Number of AHA/ACC risk factors	0.74 (0.42 to 1.31)	0.299
Indexed LVEDD, per 1 mm/m^2	0.93 (0.79 to 1.09)	0.357
Indexed LVEDD, per 1 mm/m^2	0.91 (0.77 to 1.06)	0.230
LVEF, per 1%	1.21 (0.95 to 1.53)	0.118
Multivariable models		
Model 1		
ESC SCD risk score, per 1%	1.26 (1.02 to 1.56)	0.031
Male sex	0.41 (0.11 to 1.62)	0.206
Model 2		
ESC SCD risk score, per 1%	1.05 (0.82 to 1.34)	0.705
Age at SCD event, per 1 year	0.92 (0.88 to 0.96)	<0.001
Model 3		
Age at SCD event, per 1 year	0.93 (0.89 to 0.97)	<0.001
ESC SCD risk score, per 1%	1.04 (0.81 to 1.35)	0.752
Male sex	0.55 (0.10 to 3.07)	0.495

AHA/ACC, American Heart Association/American College of Cardiology; ESC, European Society of Cardiology; LV, left ventricular; LVEDD, LV end-diastolic dimension; LVEF, LV ejection fraction; LVESD, LV end-systolic dimension; LVOT, LV outflow tract; SCD, sudden cardiac death.

including peak oxygen consumption, ventilatory efficiency, maximum workload or occurrence of ST depression (>2 mm) between groups. Notably, the occurrence of ventricular premature beats or tachycardia during CPET was lower in group 2 (table 5).

Recurrent SCD events and PA level

Twenty-three patients (30.7%) had recurrent SCD events, with no significant difference between groups (16/60 (26.7%) vs 7/15 (46.7%), p=0.234) (online supplemental table 1). However, a higher proportion of recurrent SCD events were related to high-intensity PA in group 2 (p<0.001): all seven patients in group 2 (100%) had at least one recurrent SCD event related to high-intensity PA, compared with only two out of 16 patients in group 1 (12.5%).

Risk factors of high-intensity exercise-related SCD events

On univariable regression analysis, only younger age and higher ESC SCD risk score were significantly associated with high-intensity PA during SCD events (table 6). No significant associations were noted between maximal LV wall thickness, obstructive physiology or number or presence of AHA/ACC risk factors and high-intensity PA-related SCD events. In multivariable regression models, younger age remained significantly associated with high-intensity PA-related SCD events, while the ESC SCD risk score became insignificant after adjustment for age.

Spline regression curves indicated that the OR for high-intensity PA-related SCD events decreased with age, plateauing after ~50 years (figure 2A–C). This age-related trend was preserved after adjustment for the ESC SCD risk score and sex. The OR for high-intensity PA-related SCD events tended to increase with higher ESC SCD risk score (figure 2D–F), but this association disappeared after adjustment for age.

Stratification into low-intensity, moderate-intensity and high-intensity PA groups

Analyses with stratification of the study population into three PA groups (low-intensity, moderate-intensity and high-intensity) showed consistent results: the high-intensity PA group was younger, had less extensive LGE on CMR and a tendency for higher ESC SCD risk scores (online supplemental tables 2-4). Meanwhile, there were no significant differences in clinical, morphological or genetic characteristics between the low-intensity and moderate-intensity PA groups.

DISCUSSION

This study investigated the clinical, morphological and genetic factors associated with high-intensity PA-related SCD in HCM, and found young age to be the only significant predictor, while no associations were found with traditional risk factors. Only 20% of SCD events occurred during high-intensity PA. High-intensity PA-related SCD events were associated with younger age, and all occurred under the age of 60 years. Notably, degree of LV hypertrophy, LVOT obstruction, pathogenic sarcomeric variants, ventricular arrhythmias on CPET and the number of the AHA/ACC risk factors were not associated with higher risk of SCD during high-intensity PA. Although the ESC risk score was associated with high-intensity PA-related SCD events, this association became insignificant after adjustment for age. Recurrent SCD events related to high-intensity PA occurred more frequently in survivors of high-intensity PA-related SCD. Our findings suggest that high-risk morphological features or conventional SCD risk stratification cannot be used as eligibility criteria for exercise.

Only a decade ago, patients with HCM were universally discouraged from high-intensity PA.[15 19] Previous observational studies identified HCM as a common cause of sudden death in young competitive athletes,[20] but the role of exercise as a trigger was unclear. Small retrospective autopsy studies suggested that SCDs were infrequently related to exercise in HCM.[21 22] Small randomised controlled trials showed moderate-intensity and high-intensity exercise training improved fitness without adverse events.[6 23] Recent studies reported no increase in mortality or arrhythmic events in competitive athletes continuing sports after the diagnosis of HCM.[11 12] Observational studies in large HCM cohorts showed that vigorous PA was not associated with increased mortality or SCD events,[7 8] and may even lower all-cause and cardiovascular mortality.[7] However, this does not exclude the possibility of a subset of patients with HCM more vulnerable to exercise-triggered SCD, which we aimed to investigate.

Patients experiencing SCD events during high-intensity PA were markedly younger than those with SCD events during low-intensity or moderate-intensity PA. The significant association between young age and high-intensity PA-related SCD events may be confounded by natural reduction of PA level with ageing or survivorship bias. Younger individuals are generally more active than older individuals. However, mechanistically, younger patients with dynamic myocyte growth and development may

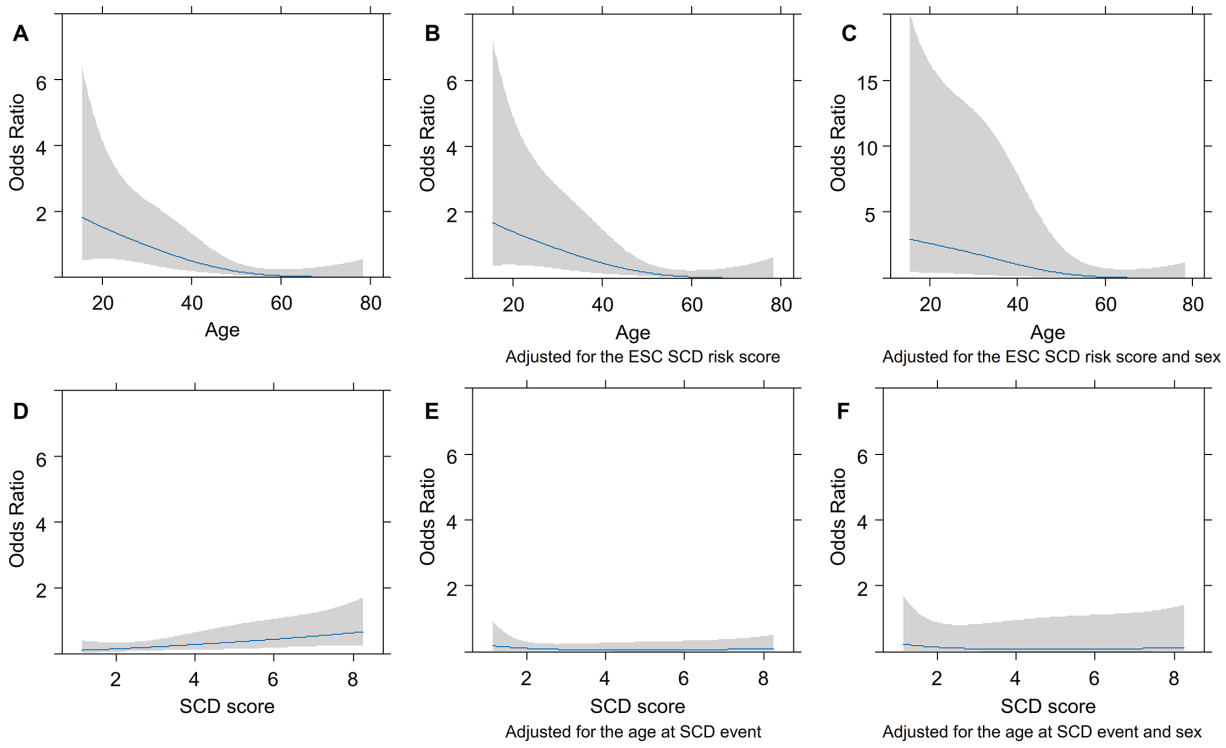

Figure 2 Association between age and the ESC SCD risk score and high-intensity physical activity-related SCD events. Spline regression curves depict the association between age (A–C) or the ESC SCD risk score (D–F) and the risk for high-intensity physical activity-related SCD events. ESC, European Society of Cardiology; SCD, sudden cardiac death.

be more susceptible to electrical instability triggered by intense physical exertion. Previous autopsy studies of patients with SCD also showed that SCD happened more frequently during exercise in children or adolescents compared with older individuals.[24 25] Furthermore, in 66 young patients with SCD and underlying HCM (aged ≤30 years), SCD during exercise was more common at younger age, especially at 10–15 years.[22] Our study showed that the proportion of exercise-related SCD decreased with age, and no high-intensity PA-related SCD events happened after 60 years of age. This observation is in line with studies showing that patients with HCM surviving or presenting past the age of 60 years have less severe disease and lower risk of SCD-related and HCM-related mortality.[26 27]

No significant differences were found in systolic or diastolic function, degree of LV hypertrophy or LVOT obstruction, or presence of apical aneurysm between PA groups. Although the overall prevalence of extensive LGE was high (42.4%) in the study cohort, none of the high-intensity PA group had extensive LGE. This can be explained by the young age of the high-intensity PA group, as LGE significantly increases over time and is less prevalent in young patients with HCM.[28] These observations indicate that morphological characteristics in HCM cannot reliably predict susceptibility to high-intensity PA-triggered SCD events. Furthermore, conventional SCD risk stratification by AHA/ACC or ESC guidelines failed to distinguish patients at higher risk for adverse outcomes during vigorous activities. The ESC SCD risk score was associated with high-intensity PA-related SCD events, but this was driven by age. Genetic testing and CPET also could not discriminate patients at higher risk of high-intensity PA-related SCD. The presence of ventricular arrhythmias on CPET was paradoxically lower in patients with high-intensity PA-related SCD events.

Meanwhile, the high proportion of recurrent SCD events related to high-intensity PA in survivors of such events emphasises the persistent risk in this subset. While the proportion of recurrent SCD events did not differ significantly between groups, recurrent events in group 2 were linked to high-intensity PA, highlighting a potential trigger mechanism in susceptible patients.

Clinical implications

ESC guidelines suggest high-intensity PA and competitive sports may be considered in asymptomatic low-risk individuals with morphologically mild HCM, but are advised against in individuals with high SCD risk, obstructive physiology or exercise-induced ventricular arrhythmias.[1] Meanwhile, AHA/ACC guidelines do not specify exercise recommendations based on morphological criteria or SCD risk, stating that high-intensity recreational PA is reasonable and competitive sports may be considered in patients with HCM after an annual comprehensive evaluation and shared decision-making.[9 10] Our study findings confirm the difficulty of identifying patients at increased risk for high-intensity PA-related SCD events, and question the validity of exercise restrictions based on 'high-risk morphological features' or conventional SCD risk stratification. Degree of LV hypertrophy, LVOT obstruction or exercise-induced ventricular arrhythmias mentioned in the guidelines were not associated with high-intensity PA-related SCD events. Younger age was the only independent risk factor, suggesting that the risk of high-intensity PA-related SCD events changes with age. These observations suggest that exercise restrictions may be unnecessary for older patients with HCM or that age-specific exercise recommendations are needed, although further studies are needed to support these postulates. Additionally, clinicians should advise

patients with previous high-intensity PA-related SCD events to refrain from vigorous exercise.

Limitations

First, the small sample size is the main limitation, which limits power to detect differences, and other significant risk factors of high-intensity PA-related SCD may have been missed. The significant association of young age with high-intensity PA-related SCD events may be confounded by aging-related reduction in PA level. Although extensive multivariable adjustment was unfeasible due to sample size, age remained significant after further adjustment for the ESC risk score. We emphasise that obtaining large numbers of patients with documented PA levels at the time of SCD events is difficult as the overall incidence of SCD events is low in HCM, and the current study population (n=75) was derived from a large HCM population (n=2619). Future multicentre and multinational cohorts will enable larger sample sizes for this special population of patients with SCD events and are required to validate our findings. Second, the retrospective nature of the study limits causality establishment. Third, PA-level classification was based on retrospective descriptions from medical records, which may be incomplete or subject to recall bias. However, fairly detailed descriptions of the PA at the SCD event could be obtained for most of the patients (n=75 of 81). Fourth, genetic testing and CPET were performed in a subset of patients, limiting conclusions on the role of specific genetic variants or exercised-induced arrhythmias in exercise-related SCD risk. Finally, future prospective studies with technology for recording continuous PA exposures over time may enable better prediction of exercise-related SCD in patients with HCM.

CONCLUSIONS

Younger age was the only significant risk factor of high-intensity PA-related SCD in this small group of patients with HCM with SCD events. Degree of LV hypertrophy or LVOT obstruction, SCD risk classification, CPET and genetics could not identify patients at increased risk of SCD during high-intensity PA. Patients with previous high-intensity PA-related SCD events should avoid vigorous exercise.

Contributors H-JL designed the study, analysed the data and drafted the manuscript. H-JL and S-YG acquired the data. KK, IC, CYS, J-WH and G-RH contributed to interpretation and critical revision of the work. All authors approved the final version. G-RH supervised the study and is responsible for the overall content as guarantor.

Funding This study was funded by Yonsei University College of Medicine (6-2023-0108).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the institutional review board (IRB) of Severance Hospital, Yonsei University Health System (4-2024-0793). Due to the retrospective design of the study, patient consent was waived by the IRB.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

ORCID iDs
Hyun-Jung Lee http://orcid.org/0000-0002-7498-0705
Seo-Yeon Gwak http://orcid.org/0000-0002-5550-4156
Chi Young Shim http://orcid.org/0000-0002-6136-0136
Jong-Won Ha http://orcid.org/0000-0002-8260-2958
Geu-Ru Hong http://orcid.org/0000-0003-4981-3304

REFERENCES

1 Arbelo E, Protonotarios A, Gimeno JR, *et al*. 2023 ESC Guidelines for the management of cardiomyopathies. *Eur Heart J* 2023;44:3503–626.
2 Reineck E, Rolston B, Bragg-Gresham JL, *et al*. Physical activity and other health behaviors in adults with hypertrophic cardiomyopathy. *Am J Cardiol* 2013;111:1034–9.
3 Sweeting J, Ingles J, Timperio A, *et al*. Physical activity in hypertrophic cardiomyopathy: prevalence of inactivity and perceived barriers. *Open Heart* 2016;3:e000484.
4 Fumagalli C, Maurizi N, Day SM, *et al*. Association of Obesity With Adverse Long-term Outcomes in Hypertrophic Cardiomyopathy. *JAMA Cardiol* 2020;5:65–72.
5 Olivotto I, Maron BJ, Tomberli B, *et al*. Obesity and its association to phenotype and clinical course in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2013;62:449–57.
6 Saberi S, Wheeler M, Bragg-Gresham J, *et al*. Effect of Moderate-Intensity Exercise Training on Peak Oxygen Consumption in Patients With Hypertrophic Cardiomyopathy: A Randomized Clinical Trial. *JAMA* 2017;317:1349–57.
7 Kwon S, Lee H-J, Han K-D, *et al*. Association of physical activity with all-cause and cardiovascular mortality in 7666 adults with hypertrophic cardiomyopathy (HCM): more physical activity is better. *Br J Sports Med* 2021;55:1034–40.
8 Lampert R, Ackerman MJ, Marino BS, *et al*. Vigorous Exercise in Patients With Hypertrophic Cardiomyopathy. *JAMA Cardiol* 2023;8:595–605.
9 Ommen SR, Mital S, Burke MA. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2020;142:e558–631.
10 Ommen SR, Ho CY, Asif IM, *et al*. 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR Guideline for the Management of Hypertrophic Cardiomyopathy: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation* 2024;149.
11 Pelliccia A, Caselli S, Pelliccia M, *et al*. Clinical outcomes in adult athletes with hypertrophic cardiomyopathy: a 7-year follow-up study. *Br J Sports Med* 2020;54:1008–12.
12 Martinez KA, Bos JM, Baggish AL, *et al*. Return-to-Play for Elite Athletes With Genetic Heart Diseases Predisposing to Sudden Cardiac Death. *J Am Coll Cardiol* 2023;82:661–70.
13 Richards S, Aziz N, Bale S, *et al*. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17:405–24.
14 Marstrand P, Han L, Day SM, *et al*. Hypertrophic Cardiomyopathy With Left Ventricular Systolic Dysfunction: Insights From the SHaRe Registry. *Circulation* 2020;141:1371–83.
15 Authors/Task Force members, Elliott PM, Anastasakis A, *et al*. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014;35:2733–79.
16 Lee H-J, Kim H-K, Lee SC, *et al*. Performance of 2020 AHA/ACC HCM Guidelines and Incremental Value of Myocardial Strain for Predicting SCD. *JACC Asia* 2024;4:10–22.
17 O'Mahony C, Jichi F, Pavlou M, *et al*. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J* 2014;35:2010–20.
18 Herrmann SD, Willis EA, Ainsworth BE, *et al*. 2024 Adult Compendium of Physical Activities: A third update of the energy costs of human activities. *J Sport Health Sci* 2024;13:6–12.
19 Gersh BJ, Maron BJ, Bonow RO, *et al*. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011;124:e783–831.
20 Maron BJ, Haas TS, Ahluwalia A, *et al*. Demographics and Epidemiology of Sudden Deaths in Young Competitive Athletes: From the United States National Registry. *Am J Med* 2016;129:1170–7.
21 Weissler-Snir A, Allan K, Cunningham K, *et al*. Hypertrophic Cardiomyopathy-Related Sudden Cardiac Death in Young People in Ontario. *Circulation* 2019;140:1706–16.
22 Finocchiaro G, Bhatia RT, Westaby J, *et al*. Sudden Cardiac Death During Exercise in Young Individuals With Hypertrophic Cardiomyopathy. *JACC Clin Electrophysiol* 2023;9:865–7.
23 MacNamara JP, Dias KA, Hearon CM Jr, *et al*. Randomized Controlled Trial of Moderate- and High-Intensity Exercise Training in Patients With Hypertrophic Cardiomyopathy: Effects on Fitness and Cardiovascular Response to Exercise. *J Am Heart Assoc* 2023;12:e031399.

24 Finocchiaro G, Radaelli D, D'Errico S, *et al*. Sudden Cardiac Death Among Adolescents in the United Kingdom. *J Am Coll Cardiol* 2023;81:1007–17.
25 Finocchiaro G, Papadakis M, Robertus JL, *et al*. Etiology of Sudden Death in Sports: Insights From a United Kingdom Regional Registry. *J Am Coll Cardiol* 2016;67:2108–15.
26 Maron BJ, Rowin EJ, Casey SA, *et al*. Risk stratification and outcome of patients with hypertrophic cardiomyopathy >=60 years of age. *Circulation* 2013;127:585–93.
27 Canepa M, Fumagalli C, Tini G, *et al*. Temporal Trend of Age at Diagnosis in Hypertrophic Cardiomyopathy: An Analysis of the International Sarcomeric Human Cardiomyopathy Registry. *Circ Heart Fail* 2020;13:e007230.
28 Axelsson Raja A, Farhad H, Valente AM, *et al*. Prevalence and Progression of Late Gadolinium Enhancement in Children and Adolescents With Hypertrophic Cardiomyopathy. *Circulation* 2018;138:782–92.