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ORIGINAL RESEARCH

Randomized Controlled Trial of Moderate- and High-Intensity Exercise Training in Patients With Hypertrophic Cardiomyopathy: Effects on Fitness and Cardiovascular Response to Exercise

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BACKGROUND: Moderate intensity exercise training (MIT) is safe and effective for patients with hypertrophic cardiomyopathy, yet the efficacy of high intensity training (HIT) remains unknown. This study aimed to compare the efficacy of HIT compared with MIT in patients with hypertrophic cardiomyopathy.

METHODS AND RESULTS: Patients with hypertrophic cardiomyopathy were randomized to either 5 months of MIT, or 1 month of MIT followed by 4 months of progressive HIT. Peak oxygen uptake (VO_2; Douglas bags), cardiac output (acetylene rebreathing), and arteriovenous oxygen difference (Fick equation) were measured before and after training. Left ventricular outflow gradient and volumes were measured by echocardiography. Fifteen patients completed training (MIT, n=8, age 52±7 years; HIT, n=7, age 42±8 years). Both HIT and MIT improved peak VO_2 by 1.3 mL/kg per min (P=0.009). HIT (+1.5 mL/kg per min) had a slightly greater effect than MIT (+1.1 mL/kg per min) but with no statistical difference (group×exercise P=0.628). A greater augmentation of arteriovenous oxygen difference occurred with exercise (Δ1.6 mL/100 mL P=0.005). HIT increased left ventricular end-diastolic volume (+17 mL, group×exercise P=0.015) compared with MIT. No serious arrhythmias or adverse cardiac events occurred.

CONCLUSIONS: This randomized trial of exercise training in patients with hypertrophic cardiomyopathy demonstrated that both HIT and MIT improved fitness without clear superiority of either. Although the study was underpowered for safety outcomes, no serious adverse events occurred. Exercise training resulted in salutary peripheral and cardiac adaptations.

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Key Words: arrhythmias ■ cardiac output ■ exercise ■ fitness ■ high intensity ■ hypertrophic cardiomyopathy ■ training

Hypertrophic cardiomyopathy (HCM) is a common, inherited cardiomyopathy defined by increased left ventricular (LV) wall thickness in the absence of, or out of proportion to, increased LV afterload.[1,2] Patients with HCM have a diverse clinical presentation, ranging from asymptomatic disease to symptomatic heart failure, due to left ventricular outflow tract (LVOT) obstruction, diastolic heart failure, or systolic

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CLINICAL PERSPECTIVE

What Is New?

- Both moderate and high intensity exercise are effective strategies to improve fitness in patients with hypertrophic cardiomyopathy, primarily by causing peripheral adaptations in oxygen use.
- High intensity exercise was associated with salutary cardiac remodeling, and no progression of patients' hypertrophic cardiomyopathy, including wall thickness or left ventricular outflow tract gradient, was observed.
- Although the study was underpowered, no serious adverse events or increase in ventricular arrhythmias were seen with training, which complements a recent large-scale observational study.

What Are the Clinical Implications?

- This study provides greater understanding of how patients with hypertrophic cardiomyopathy respond to moderate and high intensity exercise and informs the benefits and risks in shared decision making for patients with hypertrophic cardiomyopathy who are interested in high intensity exercise.

Nonstandard Abbreviations and Acronyms

a-vO_2	arteriovenous oxygen
CPET	cardiopulmonary exercise test
HCM	hypertrophic cardiomyopathy
HIT	high intensity exercise training
HR	heart rate
ILR	implantable loop recorder
MIT	moderate intensity exercise training
MSS	maximal steady state
NSVT	nonsustained ventricular tachycardia
$\dot{Q}c$	cardiac output
SCA	sudden cardiac arrest
SV	stroke volume

heart failure.[3] HCM is a known cause of sudden cardiac arrest (SCA), though mortality rates are low and only a minority of patients with HCM die of their disease.[4] Concern for SCA during exercise, particularly in young athletes, led to long-standing recommendations against competitive sports, save for sports with low intensity endurance and strength components, such as golf, yoga, etc.[5] Over the past decade, higher quality data regarding risks and benefits of exercise training in HCM have led to revised guidelines. Now mild to moderate intensity recreational exercise has a Class I indication, and high intensity exercise and competitive sports have a Class 2b recommendation with a focus on shared decision making.[1] The LIVE-HCM (Exercise in Genetic Cardiovascular Conditions) study recently demonstrated no difference in rates of SCA in patients with HCM who report vigorous exercise, providing the largest evaluation of exercise safety in HCM to date.[6] Prospective, randomized controlled data regarding the risks and benefits of exercise training remain an unmet need for patients with HCM and their clinicians.[7]

Cardiorespiratory fitness is associated with improved morbidity and mortality in patients with HCM, and fitness is best enhanced and maintained by exercise and an active lifestyle.[8] Prior recommendations against exercise have, in part, resulted in low cardiorespiratory fitness, sedentary lifestyle, low emotional well-being, and comorbidities such as obesity in many patients with HCM.[9,10] RESET-HCM (Study of Exercise Training in Hypertrophic Cardiomyopathy), the only randomized controlled trial to address exercise training in HCM, demonstrated a significant, albeit modest and variable, improvement in cardiorespiratory fitness with moderate intensity exercise without any significant clinical events.[11] Patients with HCM may want to pursue high intensity exercise training (HIT), which improves fitness more effectively than moderate intensity training (MIT) in healthy adults.[12,13] Cross-sectional studies suggest that patients with HCM who do high intensity exercise (mainly athletes) have a milder phenotype than less active patients.[14,15] However, it is likely that patients with milder phenotypes are more likely to tolerate higher intensity exercise. No prospective, randomized, controlled data assessing the efficacy and safety of high intensity exercise training in patients with HCM have been published. The goal of this study was to determine the efficacy of HIT versus MIT and to determine the underlying mechanisms of the response to exercise training in patients with HCM. We hypothesized that exercise training would improve cardiorespiratory fitness, measured as peak oxygen uptake ($\dot{V}O_2$), with a greater response in patients performing HIT compared with MIT.

METHODS

Study Design

The HIT-HCM (High Intensity Exercise for Increasing Fitness in Patients With Hypertrophic Cardiomyopathy) study was a prospective randomized clinical trial of individualized moderate intensity versus high intensity aerobic exercise training in patients with HCM performed at the Institute of Exercise and Environmental Medicine and the University of Texas Southwestern Medical Center in Dallas, Texas. Study protocols were

approved by institutional review boards at University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas. All study participants provided written informed consent. This trial was registered on ClinicalTrials.gov (NCT03335332) and was overseen by an independent data safety and monitoring board. The data that support the findings of this study are available from the corresponding author upon reasonable request. Consolidated Standards of Reporting Trials reporting guidelines were used to create this article.[16]

Recruitment occurred between 2018 and 2021 with patients referred from the University of Texas Southwestern HCM Center of Excellence or local physicians in the North Texas area. Inclusion criteria were age between 18 and 65 years with diagnosed HCM, defined as the presence of LV hypertrophy with end-diastolic wall thickness ≥15 mm or wall thickness between 13 and 15 mm with family history of HCM or positive genetic test in the absence of or out of proportion to systemic disease that can cause hypertrophy. Study exclusion criteria were exercise-induced arrhythmias, resting LVOT obstruction ≥50 mm Hg on medical therapy, recent septal reduction therapy, pregnancy, New York Heart Association IV symptoms, a hypotensive response to exercise (drop in systolic blood pressure of >20 mm Hg from resting value or during exercise), LV systolic dysfunction, prior myocardial infarction or stroke, or inability to exercise. Patients who were already performing high intensity training and athletes were excluded to avoid detraining patients if they were assigned to the moderate arm. Patients with implantable cardiac defibrillators (ICDs) previously placed at the discretion of their physician were included. A schematic of the study timeline and participant flow is shown in Figure 1. Fifty-three participants were screened, 29 consented, and 22 were randomized.

Study Procedures and Timeline

Patients underwent a baseline transthoracic echocardiogram and cardiopulmonary exercise test (CPET) with stress echocardiogram for familiarization and to screen for exercise-induced arrhythmias or evidence of inducible myocardial ischemia. At least 72 hours later, participants returned for a comprehensive CPET with a resting condition, 2 submaximal exercise steady state work rates (~40% and 60% peak $\dot{V}O_2$), and an incremental maximal exercise test, previously described.[17] CPET testing modality was matched to participants' choice of training modality with 13 participants choosing treadmill and 2 participants choosing upright cycle.

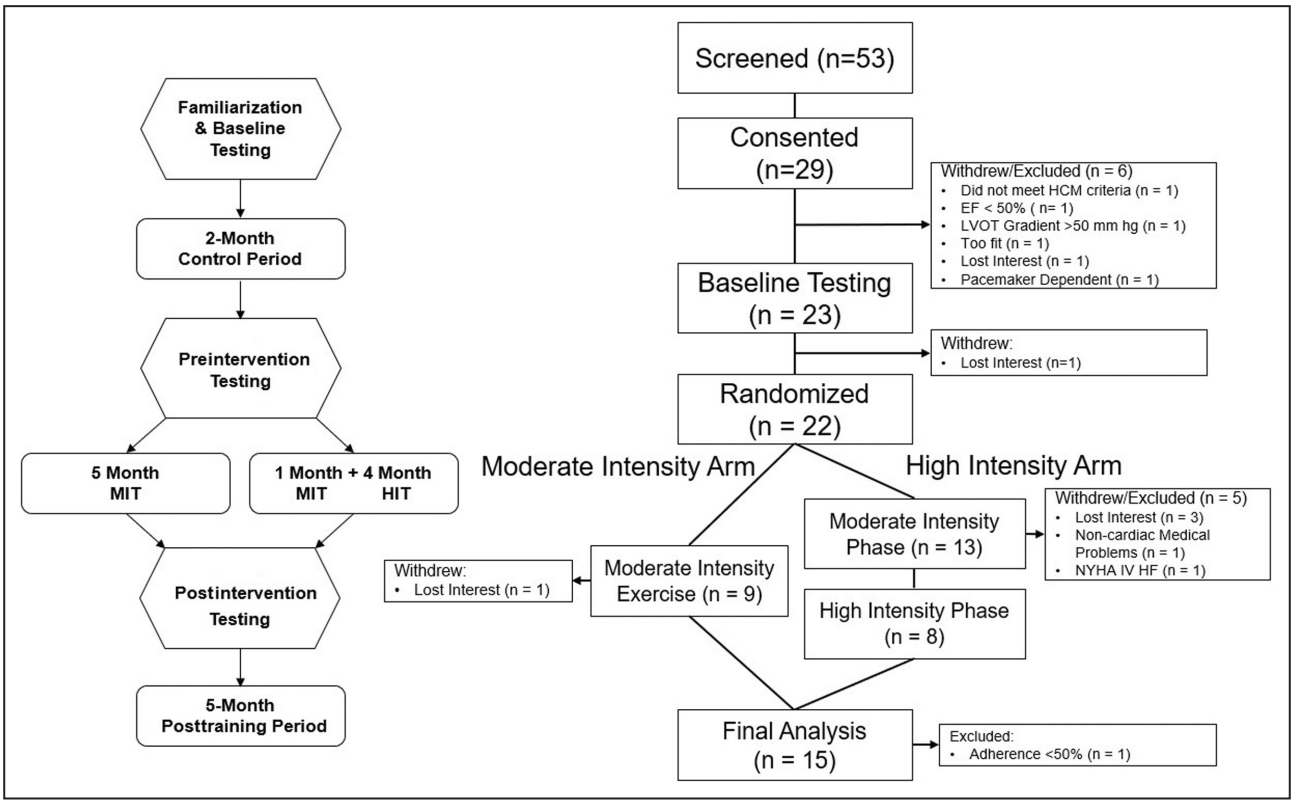

Figure 1. Overview of study design.
Schematic of study design (left) and Consolidated Standards of Reporting Trials diagram (right) showing flow of participants through the study. EF indicates ejection fraction; HCM, hypertrophic cardiomyopathy; HF, heart failure; HIT, high intensity training; LVOT, left ventricular outflow tract; MIT, moderate intensity training; and NYHA, New York Heart Association Class.

Peak exercise was tested on the treadmill used a modified Astrand-Saltin protocol, as previously described, or upright cycle ergometry with a 10 to 15 Watt increase in work rate every minute to exhaustion.[18] Cardiac output ($\dot{Q}c$), heart rate (HR), blood pressure, and $\dot{V}O_2$ were measured at each stage and during the peak exercise test. Peak $\dot{Q}c$ was measured immediately before cessation of exercise. $\dot{V}O_2$ was measured by the Douglas method, and peak $\dot{V}O_2$ was determined by the highest Douglas bag measurement of $\dot{V}O_2$ for at least 30 seconds. $\dot{Q}c$ was measured using acetylene rebreathing technique, which has been previously validated.[19] Peak LVOT gradient was measured immediately after peak exercise. Stroke volume (SV) was calculated by dividing $\dot{Q}c$ by HR. SV reserve was calculated by the percentage of increase in SV from rest to submaximal exercise. Arteriovenous oxygen (a-vO_2) difference was calculated by dividing $\dot{V}O_2$ by $\dot{Q}c$.

Echocardiography

Resting supine echocardiography was performed using Philips IE33 or Epiq 7 (Philips, Netherlands). Maximal wall thickness was measured at the site of greatest hypertrophy in the best quality parasternal or apical view with care to avoid right ventricular trabeculation or tangential measurements. LV linear measurements were performed in parasternal long axis and biplane volumetric measurements were made in standard apical views in accordance with current guidelines (Tomtec-Arena, Germany) by experienced operator blinded to patients training assignment.[20] Global longitudinal strain and early diastolic strain rate were measured as an average of peak longitudinal strain and strain rate from standard apical views (AutoStrain LV, Tomtec, Germany). Diastolic filling parameters were measured by mitral inflow (peak early diastolic filling velocity [E wave] and *E/A* ratio) and peak early diastolic recoil velocity of the mitral annulus, lateral and septal averaged to a single mean value. *E/e′* ratio was calculated using this mean e'. Continuous wave Doppler was used to assess peak gradient at rest and with valsalva.

Health-Related Measurements

Measures of body composition by dual-energy X-ray absorptiometry and quality of life (QOL) by Short Form-36 were collected before and after intervention. Hemoglobin, hematocrit, total cholesterol, low-density lipoprotein, and high-density lipoprotein were measured from venous blood.

Arrhythmia Monitoring and Control Period

After baseline testing, all participants were evaluated with continuous arrhythmia monitoring by either implantable loop recorder (ILR) or preexisting ICD. For patients with an ICD, arrhythmia detection parameters were verified by the study team and monitored throughout the study. For patients without an ICD, an ILR (Biotronik Biomonitor III) was implanted by the study team (M.S.L.) and monitored through Biotronik's Home Monitoring Service (J.P.M.). Arrhythmias detected by ILR monitoring or ICD reports during the control, training or posttraining phase were adjudicated by the study team based on electrogram tracing. Primary arrhythmias of interest included ventricular fibrillation, sustained ventricular tachycardia (>30 seconds), nonsustained ventricular tachycardia (NSVT, <30 seconds), supraventricular tachycardias, and atrial fibrillation. After baseline testing, and if needed, implantation of the ILR, participants proceeded to a 2-month control period.

Exercise Training

After their control period, participants repeated the baseline testing described here to establish preintervention values. The patients were then randomized 1:1 to moderate intensity training or high intensity training, stratified by resting LVOT gradient (<30 or ≥30) until 2020 when the COVID-19 pandemic threatened study continuation. After a brief interruption to research activity, randomization was altered to 1:3 MIT:HIT, similarly stratified by resting LVOT gradient.

Detailed training calendars are available in Figures S1 and S2. An exercise physiologist (E.I. and M.S.) met at least monthly with the participants. Their HRs were monitored remotely (Polar). HR training zones were established for each participant based on their preintervention CPET: (1) Maximal steady state (MSS) was determined from the ventilatory threshold ±5 bpm. (2) Base pace zone was 1 to 20 bpm below MSS. (3) Recovery zone was HR less than base pace zone. For participants randomized to HIT, interval zone was 90% to 95% peak HR. The first month was identical for both groups and involved 30-minute base pace sessions. Participants assigned to MIT continued base pace sessions with increased duration and volume of sessions with a maximum of 1×60 minute and 3×30 minute base pace sessions, as well as a recovery session, each week. After the first month, participants assigned to HIT started MSS sessions and began 4×4 high intensity interval sessions in month 3. The interval sessions included a 10-minute warmup period and 4 bouts of 4 minutes of exercise at 90% to 95% of their peak HR, separated by 3 minutes active rest at ~70% of their peak HR.[13] Interval sessions were directly supervised by exercise physiologist and by medical personnel with continuous ECG monitoring and available automated external defibrillator. Over the training program, the duration of base pace sessions and volume of MSS and interval sessions increased. Overall, each

HIT training participant completed 14 to 15 interval sessions over 3 months. Adherence to the training regimen was determined as the percentage of scheduled sessions completed and quality of sessions was calculated as HR achieved compared with peak HR.

Statistical Analysis and Sample Size

Statistical analysis was performed using GraphPad Prism (version 9.3.1; GraphPad Software, San Diego, CA). Descriptive data are presented as mean±SD if continuous and counts (percentages) if categorical. The primary outcome of this trial was peak $\dot{V}O_2$, measured as absolute $\dot{V}O_2$ (L/min) and normalized to body mass (mL/kg per min) and was analyzed per protocol for participants who finished the training with >50% compliance. Secondary outcomes included hemodynamic response to exercise training ($\dot{Q}c$, SV, HR, a-vO2 difference), safety outcomes (ventricular arrhythmias, sudden cardiac arrest, syncope, and supraventricular arrhythmias), echocardiographic outcomes (LV volumes, LV wall thickness, global longitudinal strain, diastolic function, and LVOT gradient) and health-related outcomes (QOL, ambulatory blood pressure, body composition, and metabolic biomarkers). To be able to detect a difference of 3.5 mL/kg per min in peak $\dot{V}O_2$ (1 MET), with an SD of 2.0 mL/kg per min at an error of 0.05 with a power of 0.80, we would need to study 12 to 14 individuals. During study design, the response of patients with HCM to HIT was unknown, and the estimated improvement in peak $\dot{V}O_2$ was derived from healthy adults.[13] Changes in parameters with exercise training were assessed by a repeated measure mixed-effects model, which included the effects of group assignment (MIT versus HIT) and time (pre versus post) as factors and their factorial (group×time) interactions terms. Time effect was used to determine the effect of exercise for the entire training cohort, and the interaction effect was used to differentiate between moderate and high intensity groups. To determine potential association of baseline fitness and response, we perform a simple linear regression between baseline fitness value and change with exercise training. *P* value <0.05 was considered statistically significant.

RESULTS

Fifteen participants completed exercise training (HIT=7, MIT=8) with >50% compliance to the training protocol. One patient was excluded from the analysis due to exercise training compliance of <50% (41%). Demographics and clinical characteristics of the participants are shown in Table 1. The participants were middle aged, and 33% identified as women. Mean body mass index was 31.0±5.7 kg/m^2, and baseline fitness level was 24.8±5.6 mL/kg per min (77% of predicted $\dot{V}O_2$max[21]) at study enrollment. A total of 33% of patients had provocable obstruction, 47% were on beta blockers, and 20% were on nondihydropyridine calcium channel blockers.

Exercise Effect

Peak $\dot{V}O_2$ response to training is shown in Table 2 and Figure 2. Exercise training improved fitness regardless of exercise intensity, with a +5% increase in peak $\dot{V}O_2$ both absolute (+104 mL/min, exercise effect=0.022) or indexed to body mass (+1.3 mL/kg per min, exercise effect=0.015). The participants who completed HIT had a numerically greater increase in their peak $\dot{V}O_2$ (+140 mL/min) compared with participants in the MIT group (+70 mL/min) but with significant variability (group×exercise=0.399). The familiarization test influenced CPET results: peak $\dot{V}O_2$ increased after the familiarization tests (+6%, *P*=0.056) but did not change after the control period (–2%, *P*=0.405). Subjects with the largest peak $\dot{V}O_2$ at baseline had the largest increase in peak $\dot{V}O_2$ with HIT training (r^2=0.56, *P*=0.053), but this association was not apparent in the MIT group (r^2=0.01, *P*=0.847). The results were not altered by the exclusion of the participant with low adherence to exercise training (exercise effect: *P*=0.031, group×exercise interaction *P*=0.552).

Mechanisms of Increased Peak $\dot{V}O_2$ With Exercise Training

Peak hemodynamic response to exercise training is shown in Table 2 and Figure 3. There was no change in peak $\dot{Q}c$, augmentation of $\dot{Q}c$ from rest to peak, or peak SV with exercise training, regardless of exercise intensity. There was a slight increase in peak a-vO_2 difference, matching the increase in peak $\dot{V}O_2$ (+5%) but with significant variability (*P*=0.129). Augmentation of a-vO_2 difference from rest to peak exercise was significantly increased after exercise training (+23%, *P*=0.013). No hemodynamic factors had a differential response to exercise intensity.

Safety End Points

Safety end points are shown in Table 3. No patients throughout the study suffered syncope, sustained ventricular tachycardia, ventricular fibrillation, or SCA. There was no significant difference in the number of patients who had NSVT or supraventricular tachycardia during the control period and the training period. Two participants had NSVT that was first detected during the training period. One participant in the HIT group had a short run (3 to 4 beats) of NSVT during exercise at the end of their training. One participant in the MIT group had several runs (6 to 8 beats) of NSVT at peak exercise in their posttraining CPET; the test was

Table 1. Demographic Information

Characteristics	Full cohort (n=15)	MIT (n=8)	HIT (n=7)	MIT vs HIT *P* value
Age, y	47.5±8.7	52.3±6.7	42.0±7.8	0.017
Women, n (%)	5 (33%)	3 (38%)	2 (29%)	0.737
Race or ethnicity, n (%)				
White Non-Hispanic	11 (73%)	7 (88%)	5 (63%)	
Hispanic	0	0	0%	
Black	1 (7%)	0	1 (13%)	
Asian	2 (13%)	1 (13%)	1 (13%)	
Native American	1 (7%)	0	1 (13%)	
Weight, kg	92.1±15.0	98.4±11.0	84.9±16.6	0.083
Body mas index, kg/m^2	31.0±5.5	32.7±5.1	29.1±5.7	0.219
Peak VO_2, mL/min per kg	24.8±5.6	24.6±4.8	25.1±6.7	0.864
% Predicted VO_2 max	77±18	83±18	70±16	0.186
Resting LVOT Gradient, mm Hg	12±10	10±7	14±13	0.390
Valsalva LVOT Gradient, mm Hg	18±15	14±10	23±19	0.275
Peak LVOT gradient, mm Hg	41±34	34±27	50±40	0.362
Obstructive hypertrophic cardiomyopathy, n (%)	5 (33%)	2 (25%)	3 (38%)	
Implantable cardiac defibrillator, n (%)	5 (33%)	5 (63%)	0	0.026
Septal reduction therapy, n (%)	4 (27%)	3 (38%)	1 (13%)	0.569
Medications				
Beta blocker, n (%)	7 (47%)	3 (38%)	4 (57%)	0.619
Nondihydropyridine calcium channel blocker, n (%)	3 (20%)	1 (13%)	2 (29%)	0.569
Diuretic, n (%)	2 (13%)	1 (13%)	1 (13%)	>0.999

Baseline characteristics of the full cohort (n=15) and patients who completed MIT and HIT are shown. Characteristics of the MIT and HIT groups were compared with unpaired *t* test, and *P* value is shown. HIT indicates high intensity training; LVOT, left ventricular outflow tract; MIT, moderate intensity training; and $\dot{V}O_2$, oxygen uptake.

terminated, and the NSVT stopped without intervention. Two participants, 1 in MIT and 1 in HIT, had NSVT detected by their ILRs that were independent of exercise, and they completed the training protocol without complication. Results of arrhythmia analysis were unaffected by participant dropout, and no participants left the study because of arrhythmia. Two participants had preexisting paroxysmal atrial fibrillation at the time of enrollment; no participants developed atrial fibrillation during the training period.

Cardiac Remodeling

Echocardiographic parameters before and after training are shown in Table 4. LV end-diastolic volume increased with high intensity training (MIT −0±8 mL versus HIT +17±15 mL, group×exercise *P*=0.015). There was no significant change in LV end-systolic volume or LV ejection fraction. Maximal wall thickness did not increase (−1±2 mm, *P*=0.09), LV end-diastolic dimension increased (+3±3 mm, *P*=0.003), and interventricular septal thickness decreased slightly (−2±2 mm, *P*=0.005) after training. Peak E wave velocity decreased slightly (−6.1 cm/s, *P*=0.043) with no change in *E/A* ratio or *E/e′* ratio. Peak gradient at rest, during valsalva, or immediately after peak exercise did not change after training.

Measures of Health

Outcomes of metabolic health are shown in Table S1. There was no change in systolic or diastolic blood pressure, measured by 24-hour ambulatory blood pressure monitoring after training. There was no change in QOL metrics. There was a small reduction in weight in the MIT group (−1.8 kg) but no change in fat mass, lean mass, or visceral fat after training in either group. There was no change in hemoglobin concentration or hematocrit, total cholesterol, low-density lipoprotein, or high-density lipoprotein after training.

Compliance

Overall, the participants trained for 23±4 weeks. The average adherence to the training protocol was

Table 2. Maximal Exercise Hemodynamic and Oxygen Uptake Responses Before and After Training

Measurement	Training group	Pretraining	Posttraining	Exercise effect	Group×exercise interaction
Peak $\dot{V}O_2$, L/min	MIT	2.31±0.41	2.38±0.47	0.022	0.399
	HIT	2.10±0.59	2.24±0.68		
Peak $\dot{V}O_2$, mL/kg per min	MIT	23.79±5.69	24.89±6.1	0.015	0.870
	HIT	25.04±7.5	26.56±8.67		
Peak $\dot{Q}_c$, L/min	MIT	14.88±2.1	14.58±3.06	0.979	0.721
	HIT	14.46±3.32	14.63±3.25		
$\Delta\dot{Q}_c$, L/min/m^2	MIT	9.97±2.01	9.61±2.65	0.346	0.975
	HIT	9.88±2.59	9.46±2.55		
Peak SV, mL	MIT	91.81±12.18	90.22±20.81	0.935	0.708
	HIT	90.51±24.67	91.3±23.26		
Peak heart rate, beats/min	MIT	162.13±6.79	163.25±6.61	0.576	0.900
	HIT	161.43±13.24	162.14±13.83		
SV reserve, %	MIT	61.76±21.61	62.18±25.24	0.431	0.402
	HIT	50.55±21.67	37.65±22.43		
Peak a-vO_2 difference, mL/100 mL	MIT	15.72±1.73	16.46±2.25	0.129	0.928
	HIT	14.51±2.73	15.21±2.49		
Δa-vO_2 difference, mL/100 mL	MIT	8.5±1.67	9.62±2.9	0.013	0.644
	HIT	7.7±2.07	9.7±2.32		
Peak systolic blood pressure, mm Hg	MIT	195.38±21.17	198.88±34.8	0.541	0.247
	HIT	182.43±20.82	171.43±19.13		
Peak diastolic blood pressure, mm Hg	MIT	83.88±18.38	89±19.09	0.874	0.283
	HIT	92.86±9.99	86±11.3		
Peak mean arterial pressure, mm Hg	MIT	121.04±12.56	125.63±18.75	0.679	0.148
	HIT	122.71±10.31	114.48±8.94		
Peak respiratory exchange ratio	MIT	1.10±0.07	1.11±0.03	0.641	0.705
	HIT	1.16±0.05	1.16±0.03		
Peak lactate, mmol/L	MIT	6.6±0.98	6.19±1.25	0.534	0.280
	HIT	7.67±2.71	7.79±2.64		

Continuous data are presented as mean±SD and were compared using 2-way ANOVA analyses. The *P* values for exercise effect and group (MIT, n=8 vs HIT, n=7) by exercise interaction are shown. a-vO_2 indicates arteriovenous oxygen; HIT, high intensity training; MIT, moderate intensity training; $\dot{Q}_c$, cardiac output; SV, stroke volume; and $\dot{V}O_2$, oxygen uptake.

86±16%. The HIT group had adherence of 72±17% to base pace sessions, 87±16% to MSS sessions, and 91±7% to the interval sessions with a mean HR of 92% of their maximal HR during intervals. MIT group had an adherence of 93±16% to base pace sessions.

DISCUSSION

In this randomized trial comparing moderate and high intensity exercise training in patients with HCM, we found that both exercise intensities were effective at improving cardiorespiratory fitness (Figure 4). Contrary to our hypothesis, clear superiority of HIT over MIT was not seen due to substantial individual variability and modest overall response to training. Numerical difference in peak $\dot{V}O_2$ of +140 mL/min in HIT group versus +70 mL/min in the MIT group was seen but did not reach conventional levels of statistical significance. Despite an increase in peak $\dot{V}O_2$, patients with HCM had no change in peak cardiac output or SV reserve, achieving increased fitness exclusively by increasing peripheral O_2 extraction. No major adverse events occurred, and nonsustained arrhythmias were balanced between the intensities and over the control and training periods. There was a significant differential response in cardiac remodeling between exercise intensities: this study showed eccentric remodeling after HIT with an increased LV end-diastolic volume and no increase in maximal wall thickness. Although sample size and patient characteristics of this study limit generalizability, the results demonstrate that patients with HCM without severe resting obstruction can improve their fitness with both moderate intensity and high intensity exercise through peripheral adaptations. The improvements in fitness with HIT were less than expected based on prior studies with healthy adults.[13]

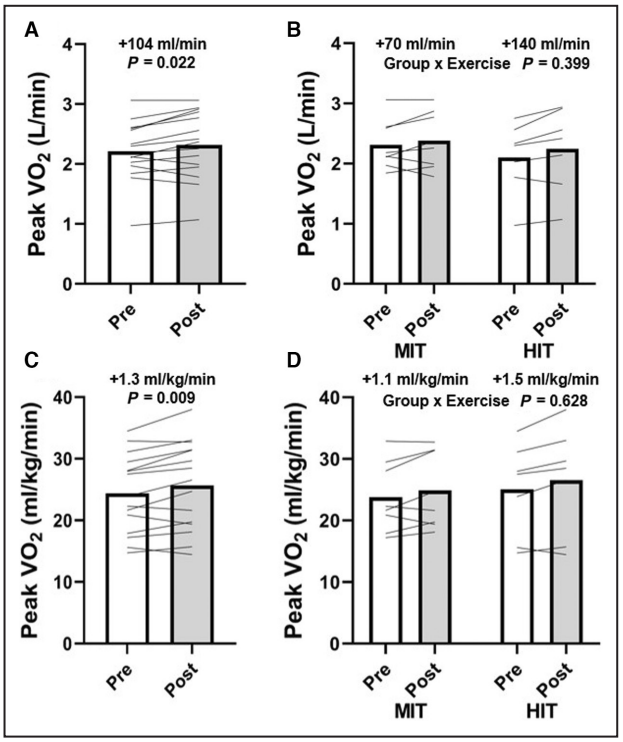

Figure 2. Primary change in fitness after exercise training. Group response in peak $\dot{V}O_2$ to exercise training, independent of intensity, is shown as absolute $\dot{V}O_2$ (**A**) and indexed to body mass (**C**). **B** and **D**, The response in peak $\dot{V}O_2$ to exercise training by intensity. Lines represent individual participant changes and bars mean value of the group. Exercise effect and group×exercise interaction of a repeated measures mixed model are shown. HIT indicates high intensity training; MIT, moderate intensity training; and $\dot{V}O_2$, oxygen uptake.

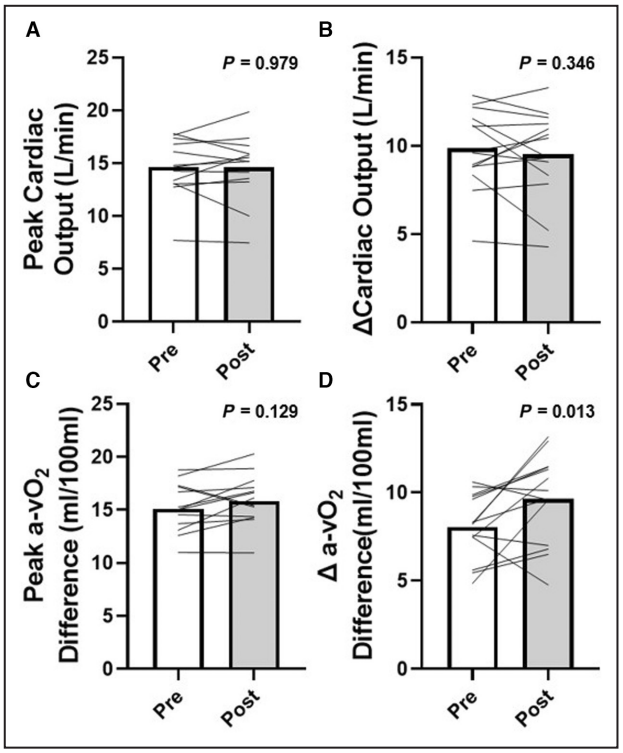

Figure 3. Cardiac and peripheral responses to exercise. Group changes in peak cardiac output (**A**), augmentation of cardiac output during peak exercise (**B**), peak arteriovenous oxygen difference, (**C**), and augmentation of arteriovenous oxygen difference during peak exercise (**D**) are shown, independent of exercise intensity. Exercise effect of repeat measures mixed model are shown.

Efficacy of Exercise Training in HCM

This study provides further evidence that exercise training is an effective modality to improve fitness in patients with HCM. Fitness is an important prognostic indicator for both morbidity and mortality in patients with HCM and has been the target of both lifestyle and pharmacologic therapies.[11,22] Currently, the most common medical therapy for patients with HCM is beta blockade, which does not improve peak $\dot{V}O_2$.[23] Novel myosin binding inhibitors are the only pharmacologic therapy that improves fitness in patients with obstructive HCM, but with limited indication and complex prescribing process.[22] In this study, exercise training was well tolerated, and both groups increased fitness with exercise training, regardless of intensity. Overall, the gain in fitness was modest, similar to that of RESET-HCM and EXPLORER-HCM (Clinical Study to Evaluate

Table 3. Safety Results

Patients with event	Moderate (n=8)			High (n=7)			*P* value
	Control period	Training period	Posttraining	Control period	Training period	Posttraining	
Sustained ventricular tachycardia, ventricular fibrillation, aborted sudden cardiac arrest	0	0	0	0	0	0	N/A
Non-SVT	3	2	3	1	2	1	0.687
SVT	1	1	1	0	0	1	0.513
Syncope	0	0	0	0	0	0	N/A

The number of patients with detected arrhythmias during preintervention control period, training period, or posttraining control periods are shown. Differences between groups over times was assessed using chi-square contingency table, and *P* values are shown. SVT indicates supraventricular tachycardia.

Table 4. Echocardiographic Data

Measurement	Training group	Pretraining	Posttraining	Exercise effect	Group×exercise interaction
Resting heart rate, bpm	MIT	78±13	77±10	0.422	0.867
	HIT	74±12	73±11		
LV end-diastolic volume, mL	MIT	141±23	140±21	0.018	0.015
	HIT	126±28	143±38		
LV end-systolic volume, mL	MIT	54±16	53±13	0.524	0.304
	HIT	42±12	46±15		
LV stroke volume, mL	MIT	86±11	87±14	0.079	0.108
	HIT	84±17	97±31		
LV ejection fraction, %	MIT	62±7	62±7	0.818	0.952
	HIT	67±4	67±7		
Maximal wall thickness, mm	MIT	23±7	23±7	0.090	0.360
	HIT	24±7	23±8		
LV diastolic dimension, mm	MIT	44±7	47±9	0.003	0.925
	HIT	38±8	41±7		
Interventricular septum diameter, mm	MIT	17±4	15±3	0.005	0.499
	HIT	20±4	18±4		
Posterior wall diameter, mm	MIT	11±1	10±2	0.141	0.376
	HIT	12±6	10±1		
Global longitudinal strain, %	MIT	–15.84±4.05	–16.34±4.28	0.815	0.509
	HIT	–16.91±1.66	–16.67±3.83		
Early diastolic strain rate, 1/s	MIT	0.69±0.14	0.68±0.17	0.838	0.989
	HIT	0.8±0.13	0.79±0.28		
S′, cm·s	MIT	7.73±1	7.83±1.15	0.539	0.356
	HIT	7.53±0.81	7.05±1.38		
E′, cm/s	MIT	6.25±0.56	5.88±1.17	0.138	0.984
	HIT	6.52±1.41	6.15±1.62		
A′, cm/s	MIT	9.98±1.98	9.08±1.89	0.114	0.242
	HIT	8.29±2.03	8.14±2.52		
E wave velocity, cm/s	MIT	77.13±27.6	75.12±31.43	0.043	0.148
	HIT	91.76±26.23	80.99±16.92		
E/A ratio	MIT	1.04±0.25	1.09±0.27	0.978	0.323
	HIT	1.29±0.52	1.23±0.57		
E/e′ ratio	MIT	12.36±4.11	13.02±5.67	0.859	0.206
	HIT	14.73±5.6	13.85±4		
Peak resting gradient, mm Hg	MIT	10.49±7.3	10.8±8.46	0.657	0.818
	HIT	11.9±4.9	12.89±11.83		
Peak valsalva gradient, mm Hg	MIT	20.88±29.71	19.06±5.05	0.517	0.286
	HIT	13.74±13.25	20.86±17.53		
Peak post exercise gradient, mm Hg	MIT	40.83±31.15	38.79±39.65	0.691	0.885
	HIT	56.71±47.89	52.87±48.6		

Continuous data are presented as mean±SD and were compared using 2-way ANOVA analyses. The *P* values for exercise effect and group (MIT, n=8 vs HIT, n=7) by exercise interaction are shown. HIT indicates high intensity training; LV, left ventricle;and MIT, moderate intensity training.

Mavacamten [MYK-461] in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy), though less than would be expected with HIT in healthy adults.[11,22] In the HIT group, patients with higher baseline fitness responded better to training than those with lower baseline fitness. Beginning training earlier in life and earlier in the progression of their HCM (ie, with milder forms of disease) may result in a greater response in fitness. Similar to RESET-HCM, exercise training did not significantly influence QOL.[11] A larger study with a tool validated for patients with HCM, such as Kansas City Cardiomyopathy Questionnaire, is

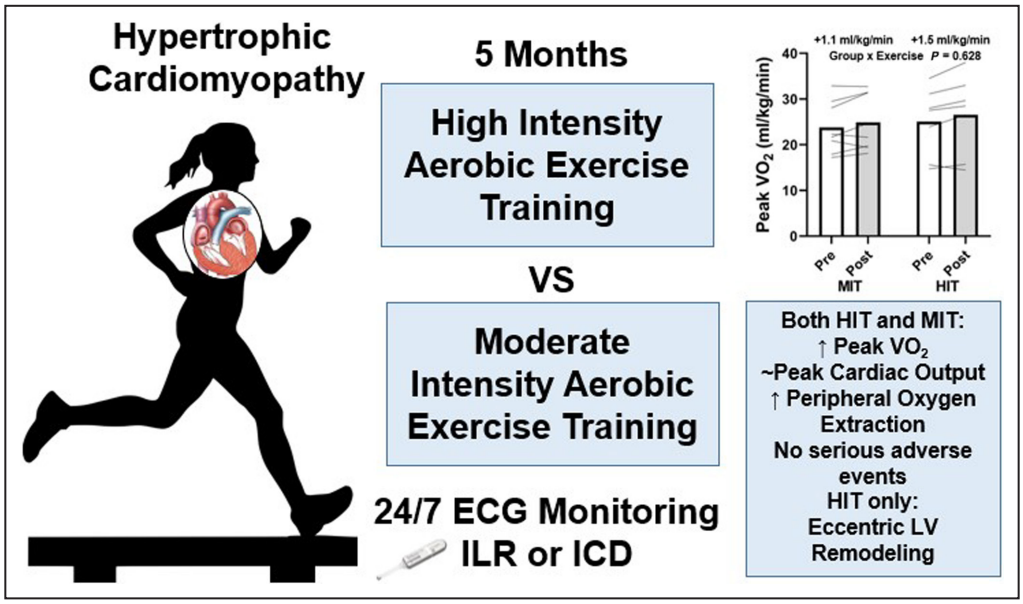

Figure 4. Summary of study results.
Summary of study design and results are shown. HIT indicates high intensity training; ICD, implantable cardiac defibrillator; ILR, implantable loop recorder; LV, left ventricular; MIT, moderate intensity training; and VO_2, oxygen uptake.

needed to determine if exercise training has a salutary benefit on the QOL for patients with HCM.[24] A critical difference in the present study compared with previous studies in this population was the inclusion of familiarization testing. During the second CPET, participants increased their peak $\dot{V}O_2$ by 6% with no intervention. The lack of familiarization testing may overestimate the gains from training. For example, if the first CPET (familiarization) and postintervention CPET were compared, the increase in peak $\dot{V}O_2$ would be 2.0 mL/kg per min, which is significantly greater than prior studies or the true training effect observed in this study. A larger study comparing MIT and HIT will be needed in the future to overcome the variability in response and elucidate its mechanisms.

Mechanisms of Improved Fitness With Exercise Training

The modest improvement in fitness despite high quality HIT may be due to the cardiac limitation to exercise in patients with HCM: 60% of patients in this study had a blunted cardiac response to metabolic demand, and 53% had an impaired SV reserve. Cardiac limitations are common among patients with HCM, and peripheral oxygen extraction is augmented in patients to maintain normal fitness.[17] Exercise training resulted in no change in peak cardiac output, peak HR, or peak SV in patients with HCM. This response is markedly different from healthy controls, where aerobic exercise training resulted in a significant increase in cardiac output and peak SV even after 3 months.[25,26] Instead, peripheral oxygen extraction increased, suggesting that a peripheral adaptation occurred with exercise training in patients with HCM.[27] In healthy adults, peripheral adaptations to HIT include increased mitochondrial capacity and upregulation in mitochondrial biogenesis.[28,29] A-vO_2 difference measured in this study does not delineate the complex process of muscle oxygen transport from the hemoglobin to ATP, and the exact mechanism of improvement remains unknown. Further studies are needed to elucidate the peripheral adaptation to exercise training in patients with HCM.

Safety

Given the rarity of SCA, this study was not powered to prove safety of HIT in patients with HCM. We carefully monitored the participants with continuous ECG monitoring and supervised interval sessions, and no serious adverse events occurred. Our careful monitoring during supervised HIT sessions complements larger population-level data, such as the LIVE-HCM study, and prior cross-sectional data to suggest that high intensity exercise may be safe for patients with HCM.[6,14,15,30] A theoretical concern exists that the hemodynamic load during exercise training may accelerate the progression of hypertrophic cardiomyopathy, leading to increased fibrosis and wall thickness through repeated increases in afterload and wall stress. However, a mouse model showed the opposite and demonstrated that if exercise was started early enough in a murine HCM model, the myofibril disarray actually can be prevented.[31] A subset of patients in RESET-HCM

underwent cardiac magnetic resonance imaging with no significant changes in cardiac structure or function.[11] The present study included echocardiograms before and after training and found no increase in maximal wall thickness or change in resting or provoked LVOT gradients. Instead, evidence of exercise induced eccentric cardiac remodeling occurred with a significant increase in LV end-diastolic volume in the patients who did HIT, similar to cardiac adaptation to HIT in healthy adults.[25] The difference in intensity with the addition of vigorous maximal state steady sessions and high intensity intervals likely caused exercise-induced remodeling where none was seen in RESET.

Limitations

This study has several limitations: The sample size was small with limited inclusion criteria and intensive testing, training, and arrhythmia monitoring. At the time of study design, high intensity exercise training carried a Class III recommendation, and thus a small and carefully performed study was an appropriate first step to evaluate this recommendation with prospective, randomized evidence. The sample size and inclusion criteria do limit the generalizability of the findings, particularly for patients with abnormal responses to exercise such as hypotension or arrhythmias. The response to HIT in this cohort of patients with HCM was lower than expected, and thus the study was underpowered to demonstrate whether HIT is superior to MIT in patients with HCM. By chance, there were significant differences between the intensity groups; the patients assigned HIT were younger, and those assigned MIT were much more likely to have ICDs. How baseline risk of SCA for patients with HCM translates to risk during exercise is unknown, but the findings of this study may not be applicable to a higher risk patient population because, by chance, few of the patients assigned to the HIIT group had ICDs. Baseline fitness was similar between the groups, but these demographic differences between the groups could have influenced the results. Finally, we cannot definitively conclude that HIT is without risk of life-threatening arrhythmias. A much larger, longer study is needed to compare the safety of HIT versus MIT in patients with HCM. The evaluation of risk of SCA in patients with HCM and the need for primary prevention ICD remains a critical aspect of patient care independent of the patients' desire to exercise.[1,32] Given the limitations of this study, an automated external defibrillator and practiced emergency action plan remain important pillars of the care of *all* athletes and patients who want to exercise.

CONCLUSIONS

This randomized controlled trial comparing moderate and high intensity exercise training in patients with HCM demonstrated that exercise training, regardless of intensity, was an effective modality to improve cardiorespiratory fitness. No serious arrhythmias, adverse clinical events, or evidence of HCM disease progression were observed with exercise training, but this study is underpowered for definitive conclusions on safety of HIT in HCM. This study provides evidence to assist clinicians in the shared decision-making process currently recommended for vigorous exercise training in patients with HCM and supports the performance of larger studies to define the role of HIT for patients with HCM.

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Disclosures

None.

Supplemental Material

Table S1
Figures S1–S2

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