JAMA | Preliminary Communication

Effect of Moderate-Intensity Exercise Training on Peak Oxygen Consumption in Patients With Hypertrophic Cardiomyopathy
A Randomized Clinical Trial

Sara Saberi, MD, MS; Matthew Wheeler, MD, PhD; Jennifer Bragg-Gresham, MS, PhD; Whitney Hornsby, PhD; Prachi P. Agarwal, MD, MS; Anil Attili, MD; Maryann Concannon, MSW; Annika M. Dries, BA; Yael Shmargad, BS; Heidi Salisbury, RN, MSN, CNS; Suwen Kumar, MBBS; Jonathan Herrera, MS; Jonathan Myers, PhD; Adam S. Helms, MD, MS; Euan A. Ashley, FRCP, DPhil; Sharlene M. Day, MD

IMPORTANCE Formulating exercise recommendations for patients with hypertrophic cardiomyopathy is challenging because of concern about triggering ventricular arrhythmias and because a clinical benefit has not been previously established in this population.

OBJECTIVE To determine whether moderate-intensity exercise training improves exercise capacity in adults with hypertrophic cardiomyopathy.

DESIGN, SETTING, AND PARTICIPANTS A randomized clinical trial involving 136 patients with hypertrophic cardiomyopathy was conducted between April 2010 and October 2015 at 2 academic medical centers in the United States (University of Michigan Health System and Stanford University Medical Center). Date of last follow-up was November 2016.

INTERVENTIONS Participants were randomly assigned to 16 weeks of moderate-intensity exercise training (n = 67) or usual activity (n = 69).

MAIN OUTCOMES AND MEASURES The primary outcome measure was change in peak oxygen consumption from baseline to 16 weeks.

RESULTS Among the 136 randomized participants (mean age, 50.4 [SD, 13.3] years; 42% women), 113 (83%) completed the study. At 16 weeks, the change in mean peak oxygen consumption was +1.35 (95% CI, 0.50 to 2.21) mL/kg/min among participants in the exercise training group and +0.08 (95% CI, −0.62 to 0.79) mL/kg/min among participants in the usual-activity group (between-group difference, 1.27 [95% CI, 0.17 to 2.37]; *P* = .02). There were no occurrences of sustained ventricular arrhythmia, sudden cardiac arrest, appropriate defibrillator shock, or death in either group.

CONCLUSIONS AND RELEVANCE In this preliminary study involving patients with hypertrophic cardiomyopathy, moderate-intensity exercise compared with usual activity resulted in a statistically significant but small increase in exercise capacity at 16 weeks. Further research is needed to understand the clinical importance of this finding in patients with hypertrophic cardiomyopathy, as well as the long-term safety of exercise at moderate and higher levels of intensity.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01127061

Editorial

Supplemental content

Author Affiliations: University of Michigan School of Medicine, Ann Arbor (Saberi, Bragg-Gresham, Hornsby, Agarwal, Attili, Concannon, Kumar, Herrera, Helms, Day); Stanford University School of Medicine, Palo Alto, California (Wheeler, Dries, Shmargad, Salisbury, Ashley); VA Palo Alto Health Care System, Palo Alto, California (Myers).

Corresponding Author: Sara Saberi, MD, MS, University of Michigan School of Medicine, 1500 E Medical Center Dr, Frankel Cardiovascular Center, Ste 2364, SPC 5853, Ann Arbor, MI 48109-5853 (saberis@med.umich.edu).

JAMA. doi:10.1001/jama.2017.2503
Published online March 17, 2017.

Hypertrophic cardiomyopathy is the most common monogenetic cardiac disease, with a prevalence of 1:200 to 1:500.[1] Most genetically defined cases are attributable to mutations in genes encoding cardiac sarcomere contractile proteins.[2] Clinically, hypertrophic cardiomyopathy is characterized by left ventricular hypertrophy in the absence of ventricular pressure overload.[3] Disease severity is markedly variable, with some individuals experiencing a normal life span with minimal complications and others carrying a high symptomatic burden.[4,5] Hypertrophic cardiomyopathy is a recognized cause of sudden cardiac death in young competitive athletes, which has prompted international consensus recommendations against competitive sports participation for all individuals with hypertrophic cardiomyopathy.[6,7]

Whether recreational exercise is associated with an increased risk of sudden cardiac death in individuals with hypertrophic cardiomyopathy is unknown. Current US and European guidelines, based solely on expert consensus, do not agree on the safety of moderate-intensity recreational exercise for patients with hypertrophic cardiomyopathy.[7,8] Survey data have shown that patients with hypertrophic cardiomyopathy are less active than the general US population, and most patients with hypertrophic cardiomyopathy report purposefully reducing their activity after diagnosis.[9] Exercise has been associated with improved survival and reduced cardiovascular morbidity and mortality in the general population.[10-13] Thus, it is important to establish evidence-based guidelines for exercise practices in patients with hypertrophic cardiomyopathy.

Exercise has been studied in patients with heart failure with preserved and with reduced ejection fraction and is effective in improving cardiorespiratory fitness as measured by peak oxygen consumption (peak $\dot{V}O_2$), which is an accurate measure of exercise capacity.[14-16] In the majority of patients with hypertrophic cardiomyopathy, peak $\dot{V}O_2$ is significantly reduced,[17] and the peak $\dot{V}O_2$ value correlates with New York Heart Association class and quality of life (QOL).[18] The goal of this study was to determine whether an individually tailored, moderate-intensity aerobic program would improve exercise capacity among patients with hypertrophic cardiomyopathy, without exacerbating disease progression or increasing the occurrence of arrhythmic events.

Key Points

Question Can moderate-intensity exercise training improve exercise capacity in patients with hypertrophic cardiomyopathy?

Findings In a randomized clinical trial of 136 patients with hypertrophic cardiomyopathy, there was a small but statistically significant increase in peak oxygen consumption in exercise group participants vs usual-activity participants at 16 weeks (+1.35 mL/kg/min vs +0.08 mL/kg/min), with no occurrences of major adverse events.

Meaning In this preliminary study involving patients with hypertrophic cardiomyopathy, moderate-intensity exercise resulted in a small increase in exercise capacity at 16 weeks. Further research is needed to understand the clinical importance of this finding, as well as to establish the long-term safety of exercise at moderate and higher levels of intensity.

Methods

Study Design

The Randomized Exploratory Study of Exercise Training in Hypertrophic Cardiomyopathy (RESET-HCM) was a randomized clinical trial of individualized moderate-intensity aerobic exercise training vs usual activity in patients with hypertrophic cardiomyopathy performed at the University of Michigan (coordinating center) and Stanford University. The institutional review boards of both centers approved the trial design (study protocol available in Supplement 1). All participants provided written informed consent before enrollment. After randomization, exercise assignment was not blinded, although study staff who collected data on study outcomes were unaware of study group assignments and all data analyses were blinded.

Recruitment took place between April 2010 and October 2015. Patients were randomized (1:1) by a single investigator blinded to patient identity (S.M.D.) to a moderate-intensity aerobic training intervention or usual activity using the minimization technique,[19] stratified by age (18-29; 30-50; >50 years), sex, and presence of left ventricular outflow tract (LVOT) obstruction at rest (LVOT peak gradient <30 mm Hg or ≥30 mm Hg). An independent data and safety monitoring board was responsible for study oversight.

Outcomes

The primary outcome was change in peak $\dot{V}O_2$ from baseline to week 16. Secondary outcomes included measures of change in cardiac remodeling, QOL, and exercise performance. Cardiac remodeling measures included magnitude of cardiac hypertrophy, left ventricular chamber dimensions, systolic and diastolic function, and scar volume as assessed by a combination of echocardiography and cardiac magnetic resonance imaging (CMR), plasma B-type natriuretic peptide concentration, and degree of LVOT obstruction.

Quality of life measures included the Minnesota Living With Heart Failure Questionnaire (MLHF) (range, 0-105; higher scores indicate worse QOL; minimal clinically important difference, 5 points), the Quick Inventory of Depressive Symptomatology-Self Report ($QIDS\text{-}SR_{16}$) (range, 0-27; higher scores indicate more severe depression), and the 36-Item Short-Form Health Survey Version 2 (SF-36v2) (8 subscales and 2 component summary scores; range, 1-100; lower scores indicate more disability; minimal clinically important difference, 3 to 5 points).

Exercise performance measures included other measures of exercise capacity, including exercise time, peak metabolic equivalent of tasks (METs), minute ventilation/carbon dioxide production ($VE/\dot{V}CO_2$) slope, and anaerobic threshold. Nonfatal arrhythmias including occurrence of nonsustained ventricular tachycardia (NSVT), atrial arrhythmias, and change in premature ventricular contraction (PVC) burden were also assessed. Major adverse events were defined as death, aborted sudden cardiac death, appropriate implantable cardioverter-defibrillator (ICD) shock, and sustained ventricular tachycardia.

Study Participants

Patients included in the study were 18 to 80 years of age and had a diagnosis of hypertrophic cardiomyopathy defined by left ventricular hypertrophy with end-diastolic wall thickness 15 mm or greater on 2D echocardiography in the absence of other primary causes of left ventricular hypertrophy or wall thickness between 13 and 15 mm in the presence of other features suggestive of hypertrophic cardiomyopathy, such as systolic anterior motion of the mitral valve leaflets, family history of hypertrophic cardiomyopathy, or positive genetic test result.[5]

Major exclusion criteria included a history of exercise-induced syncope or ventricular arrhythmias; medically refractory LVOT obstruction being evaluated for septal reduction therapy; less than 3 months after septal reduction therapy or ICD placement; history of hypotensive response with exercise testing (>20 mm Hg decrease of systolic blood pressure from baseline blood pressure or an initial increase in systolic blood pressure followed by a decrease of systolic blood pressure >20 mm Hg)[20,21]; clinical decompensation in the previous 3 months, defined as New York Heart Association class IV congestive heart failure symptoms or Canadian Cardiovascular Society class IV angina symptoms; left ventricular ejection fraction less than 55% by echocardiography; life expectancy less than 12 months; pregnant or planned pregnancy; inability to exercise owing to noncardiovascular limitations; and unwillingness to refrain from competitive sports, burst activity, or heavy isometric exercise for the duration of the study.

Study Procedures and Timeline

Baseline studies included history and physical examination, a physical activity questionnaire assessing average weekly frequency and duration of exercise sessions in the previous month, 12-lead electrocardiography, serum biomarker analysis, genetic testing (eMethods in Supplement 2), transthoracic echocardiography, CMR, cardiopulmonary exercise testing, and QOL assessment. Participants reported their sex and race/ethnicity, with options defined by the investigators (sex: male, female; race: white/Caucasian, black/African American, Asian, American Indian/Alaskan native, Native Hawaiian/Pacific Islander, Hispanic/Latino, other). Race was assessed only to provide information about the study sample and was not considered to have an association with any of the prespecified outcomes.

Patients randomized to the exercise training group participated in a structured, unsupervised exercise program individually prescribed based on heart rate reserve derived from the baseline cardiopulmonary exercise test. Exercise was initiated at a minimum of 3 sessions per week, 20 minutes per session, at a heart rate corresponding to 60% of heart rate reserve (resting heart rate +0.6 [maximal heart rate minus resting heart rate]). A rating of perceived exertion on the Borg scale[22] was used as a secondary measure of goal exercise intensity, and participants were instructed to maintain an intensity correlating to perceived exertion ratings between 11 to 14, which correlates with a moderate level of intensity. The exercise prescription was designed to increase duration of exercise by 5 to 10 minutes every week, up to 60 minutes per session, 4 to 7 sessions per week, and then incrementally increase training intensity to a goal of 70% of heart rate reserve during the first month of the study protocol. Patients were instructed to maintain their exercise regimen from weeks 5 through 16 of the protocol. Modes of exercise included cycling, walk-jog protocols, and elliptical training. No strength training or burst-type activity was prescribed. Patients in the exercise group received a 1-hour exercise consultation with a certified exercise physiologist.

Patients randomized to the usual-activity group were not provided with a formal exercise prescription at study entry and were instructed to continue their current activity practices through the duration of the study without any exercise directives. As an incentive for participation, patients in the usual-activity group were provided with an exercise consultation and exercise prescription at the conclusion of the study protocol.

All patients in both groups were provided heart rate monitors (Timex Group; Polar USA Inc) and pedometers (Omron Healthcare Inc). All patients also underwent 24 hours of continuous rhythm monitoring on enrollment, followed by automatically triggered arrhythmia detection monitoring in their first month of study participation. Adherence to the study protocol was evaluated among all participants by activity logs and weekly telephone follow-up, including the Stanford 7-day recall and downloadable data from heart rate monitors and pedometers. Physical activity data were tabulated into METs using the 2011 Compendium of Physical Activities.[23] MET-hours of activity were also calculated by multiplying METs of each activity by time spent in hours.

All patients were asked to return for evaluation 4 months after enrollment and underwent the same procedures as at the baseline visit. All electrocardiograms (investigator S.S.), echocardiograms (S.S.), CMR images (P.P.A., A.A.), cardiopulmonary exercise test studies (W.H.), and QOL surveys (S.S.) were interpreted at the coordinating center, blinded to study group assignment. Additionally, $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope at the anaerobic threshold were assessed in a random sample of 50 cardiopulmonary exercise tests (including studies from both sites) at the coordinating center by 2 interpreters (W.H. and Jacob Sitzman, BS, RCEP, CCES, University of Michigan School of Medicine), with calculated κ statistic of 0.96 and 0.79, respectively. Eleven percent of enrollment cardiopulmonary exercise tests and echocardiograms and 5% of enrollment CMRs were obtained as part of routine clinical evaluation.

Statistical Analysis

At our centers, the mean peak $\dot{V}O_2$ for patients with hypertrophic cardiomyopathy was 24 mL/kg/min at the time of the design of RESET-HCM.[24] Data from small studies of exercise training for patients with chronic heart failure available at the time of study design demonstrated an approximately 20% increase in peak $\dot{V}O_2$ with 8 to 12 weeks of exercise.[25-27] Assuming a similar effect size could be expected in patients with hypertrophic cardiomyopathy, the study was powered to detect a difference of 20% (4.8 mL/kg/min) in peak $\dot{V}O_2$ between the 2 groups with 90% power and a 2-tailed

significance of .05 or less, which required 117 participants. Assuming an attrition rate of 17% (15%-20%), the planned recruitment was increased to a total of 136 patients.

Statistical analyses were performed by the coordinating center using SAS software version 9.3 (SAS Institute). Statistical comparisons of the study groups with respect to clinical outcomes were performed according to the intention-to-treat principle. Patient characteristics are expressed as mean (SD) or median (interquartile range) for continuous variables and frequencies and percentages for categorical variables. Change in patient characteristics over time were performed using the *t* test for continuous variables and χ^2 or Fisher exact test for categorical variables. The Kruskal-Wallis test was used for testing differences in medians. Data that were not normally distributed were log transformed for statistical analysis. The primary efficacy analysis was performed using analysis of variance and linear regression, with baseline peak $\dot{V}O_2$ value as covariate. A secondary analysis of the effect of exercise training was performed using multiple linear regression with the baseline value of the outcome measure, site, and genetic status as covariates.

A post hoc sensitivity analysis of the primary outcome was performed by multiple imputation with 10 interactions on all patients randomized by using demographics, baseline characteristics, baseline comorbidities, and baseline cardiopulmonary exercise test parameters. Linear regression was performed on the change in peak $\dot{V}O_2$, adjusting for baseline value. In additional post hoc analyses, submaximal exercise studies, defined as those with peak respiratory exchange ratio less than 1.05, were removed from the primary end point analysis and analysis of variance was performed. To control for variability in peak effort, $\dot{V}O_2$ attained at respiratory exchange ratio 1.0 was analyzed by group. Comparison of the PVC burden over time also was performed.

Statistical significance was set at $P < .05$ using 2-sided tests for the assessment of the primary outcome. Analyses of outcomes for cardiac remodeling, QOL, and secondary measures of exercise performance were not adjusted for multiple comparisons and therefore are considered exploratory and hypothesis generating.

Results

Patient Characteristics

During a 5-year period, 728 adult patients with hypertrophic cardiomyopathy were screened for trial eligibility (**Figure 1**), and 136 participants (16.9% with obstructive hypertrophic cardiomyopathy; 42% women; mean age, 50.4 [SD, 13.3] years) were randomized into exercise training and usual-activity groups. Baseline characteristics of patients in each group are shown in **Table 1**. All but 1 of the participants who completed the protocol underwent genetic testing. Baseline clinical characteristics did not change over time (eTable 1 and eTable 2 in Supplement 2). The attrition rates in the exercise training and usual-activity groups were comparable at 16 weeks (14.9% vs 18.8%, respectively, $P = .54$). Baseline clinical characteristics between participants who completed the study compared with those who withdrew from the study were also similar (eTable 3 in Supplement 2).

Primary End Point

At 16 weeks, mean change in peak $\dot{V}O_2$ was +1.35 (95% CI, 0.50 to 2.21) mL/kg/min among participants in the exercise training group and +0.08 (95% CI, −0.62 to 0.79) mL/kg/min among participants in the usual-activity group (between-group difference, 1.27 [95% CI, 0.17 to 2.37] mL/kg/min) (**Figure 2**), representing an absolute increase of 6% (95% CI, 1.27% to 22.7%) compared with baseline values. Adjustment for baseline genetic status and study site did not attenuate the improvement in peak $\dot{V}O_2$ observed in the exercise training group compared with the usual-activity group (difference in increase in peak $\dot{V}O_2$ of +1.29 mL/kg/min [95% CI, 0.20 to 2.38 mL/kg/min]; $P = .02$).

Exploratory End Points

Measures of Cardiac Remodeling

There were no significant differences between the exercise training group vs the usual-activity group at 16 weeks in terms of changes in any measures of cardiac morphology or function (eTable 4 in Supplement 2), in LVOT gradient (eTable 4 in Supplement 2), or in serum B-type natriuretic peptide levels (eTable 2 in Supplement 2).

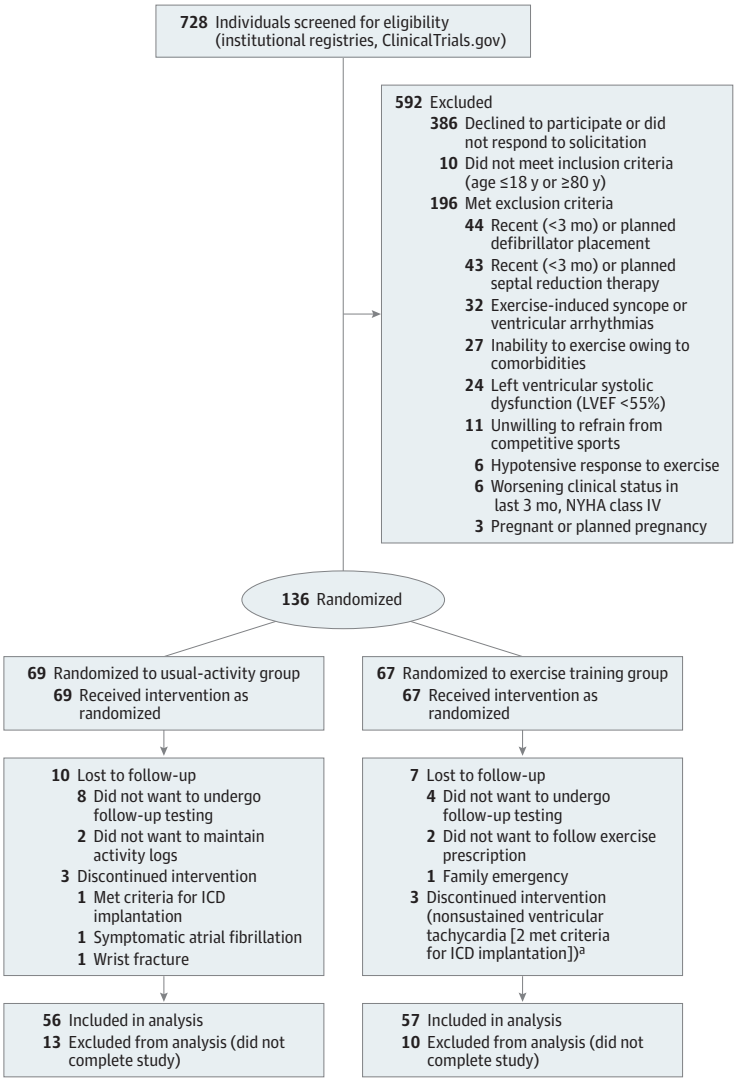
Quality of Life

Among the outcomes examining effects of exercise training on QOL, there were no significant differences between the exercise group and the usual-activity group at 16 weeks in terms of 9 scores of the SF-36v2 subscales, the QIDS-SR_{16} score, or 3 scores on the MLHF measures. The only significant difference between groups was for the SF-36v2 physical functioning scale (increase of 5.7 points in the exercise group and decrease of 2.5 points in the usual-activity group; difference, +8.2 points [95% CI, 2.6 to 13.7 points]) (eTable 5 in Supplement 2).

Exercise Performance

Based on physical activity surveys completed at the time of study initiation, there were no significant differences between the groups in the weekly average time spent exercising. Prior to enrollment, 66 participants in the usual-activity group and 65 in the exercise training group responded to a survey of current exercise habits. Twenty-seven (41%) of the participants in the usual-activity group and 29 (45%) in the exercise training group reported no regular exercise. Of those who did report regular exercise, the majority walked (25/39 [64.1%] in the usual-activity group, 26/36 [72.2%] in the exercise training group). During the study protocol, 7 of 28 (28%) participants in the usual-activity group and 26 of 28 (93%) in the exercise training group who reported no prior history of regular exercise engaged in regular weekly exercise. During the study, participants in the exercise training group exercised a mean of 1.5 days more per week than those in the usual-activity group (3.6 days vs 2.1 days) and spent more time engaged in intentional exercise (eTable 6 in Supplement 2). The most common modes of exercise during study participation were walking, jogging/running, swimming, elliptical use, and cycling.

Figure 1. Flow of Participants Through the Study



ICD indicates implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction.

[a] Two patients had prior history of nonsustained ventricular tachycardia (NSVT). One had NSVT on day 1 after enrollment before starting the exercise program and was referred for implantable cardioverter-defibrillator (ICD) implantation; the other had NSVT unrelated to exercise and already had an ICD. One patient with no prior history of NSVT had an episode of NSVT on day 13 of the protocol, 1 hour after exercising, and was referred for ICD implantation.

Participants in the exercise group had a greater change in peak workload: 0.38 METs for exercise training vs 0.03 METs for usual activity (difference, 0.36 [95% CI, 0.05 to 0.67]) (eFigure 1A in Supplement 2).

Post Hoc Analyses

Sensitivity Analyses of the Primary Outcome Peak $\dot{V}O_2$

In a sensitivity analysis of the primary outcome, performed using multiple imputation and including all participants in the trial (n = 136), the mean change in peak $\dot{V}O_2$ was +1.50 mL/kg/min (95% CI, −5.1 to 8.1 mL/kg/min) in the exercise training group and +0.17 mL/kg/min (95% CI, −5.4 to 5.7 mL/kg/min) in the usual-activity group (difference, 1.22 mL/kg/min [95% CI, 0.09 to 2.35 mL/kg/min], adjusting for baseline peak $\dot{V}O_2$).

Additional Post Hoc Analyses

When CPET studies with peak respiratory exchange ratio (RER) less than 1.05 (indicating less than maximal effort [n = 13]) were removed from the analysis, the change in peak $\dot{V}O_2$ was +1.36 mL/kg/min in the exercise training group and +0.06 mL/kg/min in the usual-activity group (between-group difference, 1.30 mL/kg/min [95% CI, 0.15 to 2.45 mL/kg/min]). Adjustment for the baseline peak $\dot{V}O_2$ did not attenuate the difference in peak $\dot{V}O_2$ observed in the exercise training group vs the usual-activity group (between-group difference, 1.18 [95% CI, 0.10 to 2.26]). In analyses controlling for variability in peak effort, $\dot{V}O_2$ attained at respiratory exchange ratio 1.0, the mean change in $\dot{V}O_2$ at the same level of effort was +1.17 mL/kg/min (95% CI, 0.19 to 2.15) in the exercise training group and −0.09 mL/kg/min (95% CI, −0.75 to 0.57) in the usual-activity group (difference, 1.26 mL/kg/min [95% CI, 0.09 to 2.43]) (eFigure 1B in Supplement 2). Additionally, a significant reduction in PVC burden was observed in the exercise group (−0.43 [95% CI, −1.06 to 0.20] PVC/h vs 0.48 [95% CI, −0.12 to 1.08] PVC/h; difference, −0.91 [95% CI, −1.76 to −0.05] PVC/h; estimates calculated from log-transformed data).

Table 1. Demographic and Clinical Characteristics at Baseline

Variable	Usual Activity (n = 69)	Exercise (n = 67)
Demographic and physical characteristics		
Age, mean (SD), y	50.0 (13.5)	50.5 (13.2)
Women, No. (%)	28 (40.6)	29 (43.3)
Race/ethnicity, No. (%)		
White	63 (91.3)	56 (83.6)
Other[a]	6 (8.7)	11 (16.4)
Weight, mean (SD), kg	92.6 (15.7)	90.5 (18.3)
BMI, mean (SD)	31.4 (5.1)	30.6 (5.6)
Waist-hip ratio, mean (SD)	0.91 (0.14)	0.93 (0.10)
Peak $\dot{V}O_2$, mean (SD), mL/kg/min	22.5 (7.2)	21.3 (6.3)
Echocardiographic imaging		
Maximal LV wall thickness, mean (SD), mm	21 (6)	21 (5)
Obstruction at rest, No. (%)[b]	12 (17.4)	11 (16.4)
Peak LVOT pressure gradient, mean (SD), mm Hg		
At rest	20.7 (27.2)	15.2 (14)
With Valsalva[c]	31.8 (37.3)	23.6 (24.6)
After exercise[d]	57.0 (51.9)	48.1 (43.5)
Left atrial size, mean (SD), mm[e]	44.5 (5.8)	43.2 (7.7)
Left atrial volume index, mean (SD), mL/m^2	46.1 (14.3)	47.4 (15.6)
Diastolic dysfunction, No. (%)[e,f]		
Grade I	49 (71)	48 (72.7)
Grade II-III	20 (29)	18 (27.3)
RVSP, mean (SD), mm Hg[g]	27.7 (10.1)	28.7 (10.1)
LVEF, mean (SD), %	70.8 (4.3)	70.6 (4.0)
Cardiac magnetic resonance imaging, mean (SD)		
Maximal LV wall thickness, mm[h]	19 (5)	18 (4)
LV mass index, g/m^{2h}	78.9 (28.0)	73.5 (20.1)
LV EDV index, mL/m^{2i}	83.9 (14.4)	79.4 (12.4)
LV ESV index, mL/m^{2i}	29.1 (9.1)	29.6 (8.4)
LVEF, %[i]	65.7 (7.0)	62.7 (6.9)
Total DGE mass, g[j]	4.9 (10.3)	4.7 (6.7)
DGE % of LV mass, %[j]	2.9 (5.0)	3.1 (3.8)
Morphology, No. (%)		
Asymmetric interventricular septal hypertrophy		
Reverse curve	32 (46.4)	35 (52.2)
Neutral	20 (29.0)	16 (23.9)
Sigmoid	6 (8.7)	6 (9.0)
LV hypertrophy		
Concentric	2 (2.9)	3 (4.4)
Mid-cavity with apical aneurysm	4 (5.8)	1 (1.5)
Apical	5 (7.2)	6 (9.0)
NYHA class, No. (%)		
I	46 (66.7)	44 (65.7)
II-III	23 (33.3)	23 (34.3)
BNP, median (IQR), pg/mL	83 (38-200)	79 (27-186)
Creatinine, mean (SD), mg/dL	0.92 (0.17)	0.94 (0.23)
ICD, No. (%)	21 (30.4)	25 (37.3)

(continued)

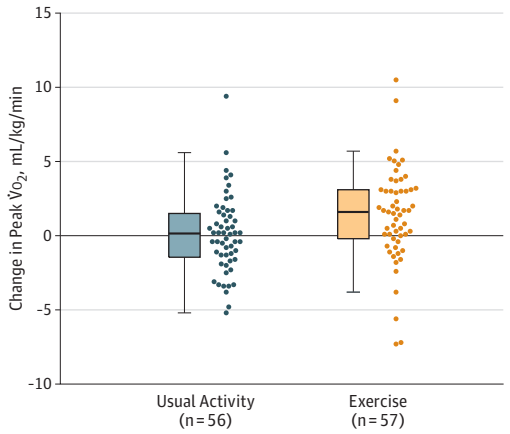
Table 1. Demographic and Clinical Characteristics at Baseline (continued)

Variable	Usual Activity (n = 69)	Exercise (n = 67)
Cardiac history, No. (%)		
VT, VF, or aborted SCD	2 (2.9)	3 (4.5)
NSVT	10 (14.5)	9 (13.4)
AF	8 (11.6)	14 (20.9)
SVT	3 (4.3)	1 (1.5)
PVC burden, No. per hour (SD)	13.5 (26.3)	19.2 (56.4)
Septal reduction procedure	15 (21.7)	20 (29.9)
Comorbid conditions, No. (%)		
Hypertension	16 (23.2)	14 (20.9)
Coronary artery disease	6 (8.7)	3 (4.5)
Diabetes mellitus	5 (7.2)	4 (6.0)
Lung disease	3 (4.3)	1 (1.5)
Depression or anxiety	7 (10.1)	6 (9.0)
Medications, No. (%)		
β-Blocker	51 (73.9)	41 (61.2)
Calcium channel blocker	14 (20.3)	15 (22.4)
Disopyramide	3 (4.3)	1 (1.5)
Diuretic	11 (15.9)	8 (11.9)
ACE inhibitor/ARB	9 (13.0)	8 (11.9)
Antiplatelet agent	25 (36.2)	27 (40.3)
Anticoagulant	9 (13.0)	8 (11.9)
Antiarrhythmic agent	3 (4.3)	5 (7.5)
Statin	22 (31.9)	19 (28.4)
Antidepressant	8 (11.6)	6 (9.0)
Sarcomere mutation, No. (%)[k]		
No testing	1 (1.5)	5 (7.5)
Pathogenic	25 (36.2)	33 (49.3)
Variant of uncertain significance	6 (8.7)	8 (11.9)
Negative	37 (53.6)	21 (31.3)

Abbreviations: ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BNP, B-type natriuretic peptide; CMR, cardiac magnetic resonance imaging; DGE, delayed gadolinium enhancement; EDV, end-diastolic volume; ESV, end-systolic volume; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LV, left ventricular; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; PVC, premature ventricular contraction; RVSP, right ventricular systolic pressure; SCD, sudden cardiac death; SVT, supraventricular tachycardia; VF, ventricular fibrillation; $\dot{V}O_2$, oxygen consumption; VT, ventricular tachycardia.
SI conversion factor: To convert creatinine values to µmol/L, multiply by 88.4.

[a] Other includes black, Hispanic, Asian, other/unknown.
[b] Defined as resting left ventricular outflow tract peak pressure gradient 30 mm Hg or greater.
[c] Usual activity n = 60, exercise n = 60.
[d] Usual activity n = 68, exercise n = 66.
[e] Usual activity n = 69, exercise n = 66.
[f] Diastolic dysfunction severity determined according to American Society of Echocardiography criteria.
[g] Usual activity n = 63, exercise n = 59.
[h] Usual activity n = 41, exercise n = 36.
[i] Usual activity n = 40, exercise n = 36.
[j] Usual activity n = 30, exercise n = 28.
[k] Genetic testing included the sequencing of at least 9 sarcomere genes (eMethods in Supplement 2). Patients were classified as having a pathogenic mutation if at least 1 disease-causing mutation in 1 of the 9 genes was identified. Variants were considered of uncertain significance if they could not be definitely classified as either disease-causing or benign. Patients negative for sarcomere mutations did not have any variants identified in any of the 9 sarcomere genes.

Figure 2. Change in Peak Oxygen Consumption From Baseline to 16-Week Follow-up



Dark horizontal lines indicate median values, and the top and bottom of the boxes represent the 75th and 25th percentiles, respectively. The top and bottom whiskers represent the 97.5th and 2.5th percentiles, respectively. Individual data points are also shown. *P* = .02 for the difference between groups.

Table 2. Adverse Events Experienced During Study Protocol

Variable	No. (%) Usual Activity (n = 69)	No. (%) Exercise (n = 67)
Nonsustained ventricular tachycardia[a]	15 (23.1)	19 (31.7)
Atrial fibrillation[a]	7 (11.5)	5 (8.8)
Supraventricular tachycardia[a]	29 (47.5)	23 (40.3)
Syncope	2 (2.9)	0
Musculoskeletal injury		
Minor[b]	1 (1.4)	0
Major[c]	2 (2.9)	3 (4.5)

[a] Usual activity n = 61, exercise n = 57 (number in each group with arrhythmia detection monitoring data).

[b] Minor musculoskeletal injury defined as mild or moderate discomfort.

[c] Major musculoskeletal injury defined as persistent incapacity.

Adverse Events

There were no occurrences of major adverse events, including death, aborted sudden cardiac death, appropriate ICD shocks, or sustained ventricular tachycardia in either group. Exercise training was not associated with an increased occurrence of any nonfatal arrhythmias (**Table 2**).

Three participants in the exercise group were withdrawn from the study after randomization because of symptomatic NSVT. All 3 were withdrawn based on the recommendations of the data and safety monitoring board. One patient who had a history of NSVT experienced 30 seconds of NSVT on day 1 after enrollment, prior to starting the exercise program, and was referred for ICD implantation. A second patient with a history of NSVT who already had an ICD implanted experienced more frequent episodes of symptomatic NSVT unrelated to exercise. The third patient had no history of NSVT and experienced a 28-beat run of NSVT on day 13 of the protocol, 1 hour after exercising, and was referred for ICD implantation.

Discussion

In this preliminary study involving patients with hypertrophic cardiomyopathy, moderate-intensity exercise compared with usual activity resulted in a statistically significant but small increase in exercise capacity at 16 weeks. No major adverse effects occurred, and there was no difference between the groups in rates of nonsustained ventricular arrhythmias or atrial fibrillation. Analyses of other outcomes of cardiac remodeling, QOL, and exercise performance revealed no differences between the exercise training group and usual-activity group, except for improvement of scores on QOL physical function scale, peak METs on cardiopulmonary exercise test, and PVC burden favoring the exercise group. However, these findings were not adjusted for multiple comparisons and therefore should be interpreted cautiously and should be considered exploratory and hypothesis generating.

The findings from this randomized clinical trial provide support for moderate-intensity aerobic exercise for improving exercise capacity in patients with hypertrophic cardiomyopathy. The magnitude of improvement in peak $\dot{V}O_2$ was modest, with an absolute increase of 1.27 (95% CI, 0.17 to 2.37) mL/kg/min in the exercise training group compared with the usual-activity group, representing an absolute increase of 6% (95% CI, 1.27% to 22.7%). In the largest study of exercise in patients with heart failure (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training [HF-ACTION]),[15,28] the exercise intervention was associated with an absolute increase in peak $\dot{V}O_2$ of 0.6 mL/kg/min (95% CI, 0.43 to 0.77), or 4%.[15] In HF-ACTION, every 6% increase in peak $\dot{V}O_2$ was associated with an 8% lower risk for cardiovascular mortality or heart failure hospitalizations.[29]

Moderate-intensity aerobic exercise improves overall cardiovascular health and survival in the general population.[11-13,30] Because hypertrophic cardiomyopathy is a recognized cause of sudden cardiac death in young competitive athletes, there is uncertainty about whether lower-intensity exercise could predispose these patients to a similar risk. In the absence of evidence to the contrary, many physicians caring for patients with hypertrophic cardiomyopathy recommend extremely conservative physical activity restrictions, and many patients are fearful of engaging in exercise at any level.[31] Despite the need for data to inform such recommendations,[7,8] to our knowledge, no clinical trial has previously implemented an exercise intervention in patients with hypertrophic cardiomyopathy.[32]

The current study demonstrates the feasibility of implementation of a 16-week structured exercise program for patients with hypertrophic cardiomyopathy, with no major adverse events observed in either group. The study population included a substantial percentage of higher-risk individuals, with more than 30% of patients having defibrillators and 4% having a prior history of sustained ventricular tachycardia or aborted sudden cardiac arrest.

Reduced peak $\dot{V}O_2$ has been shown to correlate with clinical decompensation and mortality in hypertrophic cardiomyopathy.[33-35] No medications or interventions have yet been shown to improve peak $\dot{V}O_2$ in patients with hypertrophic cardiomyopathy. This study provides preliminary support for a regimen of unsupervised brisk walking 4 to 7 days per week for a minimum of 30 minutes, as a targeted intervention for patients with hypertrophic cardiomyopathy. This study also provides the rationale for future studies examining longer-term outcomes related to exercise training in this population.

The individualized exercise prescriptions in this study did not exceed a level considered within acceptable limits for recreational exercise for patients with hypertrophic cardiomyopathy.[8] Yet participants in the exercise training intervention exercised more frequently and purposefully than those in the usual-activity group, suggesting that an exercise consultation to establish an individualized exercise training program for patients with hypertrophic cardiomyopathy may be considered in clinical practice to promote a healthy, active lifestyle.

Limitations

This study has several limitations. First, there is a potential for sampling bias, because 386 of 728 potential study participants declined to participate and another 206 were excluded. However, the clinical characteristics of the patients enrolled in this study were similar to characteristics in the entire cohorts at our respective institutions, as well as those in published series from other institutions.[33,36]

Second, the effect size of exercise training in patients with hypertrophic cardiomyopathy was relatively modest and was substantially less than the anticipated effect size on which the study was powered (ie, 20% relative improvement, absolute improvement of 4.8 mL/kg/min in peak $\dot{V}O_2$ in the exercise training group compared with the usual-activity group). The anticipated effect size was based on small studies of exercise training in patients with heart failure who were available at the time of study design.[25-27] Since then, the largest exercise training study in patients with heart failure, HF-ACTION, demonstrated a much more modest relative improvement in peak $\dot{V}O_2$ (median, 4% increase).[15]

Third, although there were no major adverse events and no signal for harm in any of the participants, the study was not powered to assess safety of the exercise intervention. Such a study would require a substantial sample size, given the relative rarity and infrequency of major adverse events in patients with hypertrophic cardiomyopathy compared with those with chronic heart failure.[4] While there was no evidence that exercise-induced hypertrophic or fibrotic remodeling, future studies with longer follow-up will be required to assess any potential influence of exercise on disease progression.

Fourth, because of the nature of the intervention, it was not possible to blind patients to treatment assignment. In the absence of blinding, self-reported QOL scores may be biased by patient expectations.

Fifth, the exercise prescription used in this study only incorporated moderate-intensity aerobic exercise in adult patients. Future studies will need to address the safety and benefits of more vigorous aerobic exercise and isometric activities, including participation in competitive sports, in both adult and pediatric patients with hypertrophic cardiomyopathy.

Conclusions

In this preliminary study involving patients with hypertrophic cardiomyopathy, moderate-intensity exercise compared with usual activity resulted in a statistically significant but small increase in exercise capacity at 16 weeks. Further research is needed to understand the clinical importance of this finding in patients with hypertrophic cardiomyopathy, as well as the long-term safety of exercise at moderate and higher levels of intensity.

ARTICLE INFORMATION

Published Online: March 17, 2017. doi:10.1001/jama.2017.2503

Author Contributions: Drs Saberi and Day had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Saberi, Wheeler, Salisbury, Myers, Ashley, Day.
Acquisition, analysis, or interpretation of data: Saberi, Wheeler, Bragg-Gresham, Hornsby, Agarwal, Attili, Concannon, Dries, Shmargad, Salisbury, Kumar, Herrera, Helms, Ashley, Day.
Drafting of the manuscript: Saberi, Hornsby, Dries, Myers, Ashley, Day.
Critical revision of the manuscript for important intellectual content: Saberi, Wheeler, Bragg-Gresham, Agarwal, Attili, Concannon, Shmargad, Salisbury, Kumar, Herrera, Myers, Helms, Ashley, Day.
Statistical analysis: Saberi, Bragg-Gresham, Myers, Ashley.
Obtained funding: Saberi, Salisbury, Day.
Administrative, technical, or material support: Saberi, Hornsby, Agarwal, Attili, Concannon, Dries, Salisbury, Kumar, Ashley.
Supervision: Saberi, Wheeler, Ashley, Day.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Funding/Support: This study was supported by research grant UL1TR000433 from the Michigan Institute for Clinical & Health Research, the University of Michigan Frankel Cardiovascular Center McKay Research Grant, the University of Michigan Frankel Cardiovascular Center Inaugural Grant, and an anonymous donor. The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Meeting Presentation: Presented at the American College of Cardiology 66th Annual Scientific Session; March 17, 2017; Washington, DC.

Additional Contributions: We thank Keith E. Kocher, MD, MPH (University of Michigan School of Medicine), for assistance in preparing and reviewing the manuscript and John G. Younger, MD (Argo Pond LLC), for assistance with data analysis. We thank study coordinators Brice Rolston, MD, MBA, Scott Baty, Wendi Schumacher, and Linda C. Baty, MSN, RN, NP-C (University of Michigan School of Medicine), for assistance in the recruitment process and data entry; Matthew Kolevar, BSE (University of Michigan), for assistance with data entry; Sonya Clark (University of Michigan School of Medicine) for administrative support; Jacob Sitzmann, BS, RCEP, CCES, for assistance with data analysis; Kara Eggerbrecht, BS, CEP, and Jennifer Richichi, BS, CEP (University of Michigan), for performing cardiopulmonary exercise test studies. Mr Sitzman and Mr Kolevar received compensation for their contributions; no other persons named received compensation, apart from their employment at the study coordinating center.

REFERENCES

1. Semsarian C, Ingles J, Maron MS, Maron BJ. New perspectives on the prevalence of hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2015;65(12):1249-1254.

2. Alcalai R, Seidman JG, Seidman CE. Genetic basis of hypertrophic cardiomyopathy: from bench to the clinics. *J Cardiovasc Electrophysiol*. 2008;19(1):104-110.

3. Braunwald E, Lambrew CT, Rockoff SD, Ross J Jr, Morrow AG. Idiopathic hypertrophic subaortic stenosis, I: a description of the disease based upon an analysis of 64 patients. *Circulation*. 1964;30(suppl 4):3-119.

4. Maron BJ, Casey SA, Poliac LC, Gohman TE, Almquist AK, Aeppli DM. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. *JAMA*. 1999;281(7):650-655.

5. Gersh BJ, Maron BJ, Bonow RO, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; American Association for Thoracic Surgery; American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Failure Society of America; Heart Rhythm Society; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;124(24):2761-2796.

6. Maron BJ, Udelson JE, Bonow RO, et al; American Heart Association Electrocardiography and Arrhythmias Committee of Council on Clinical Cardiology, Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and American College of Cardiology. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: task force 3: hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and other cardiomyopathies, and myocarditis: a scientific statement from the American Heart Association and American College of Cardiology. *Circulation*. 2015;132(22):e273-e280.

7. Pelliccia A, Corrado D, Bjørnstad HH, et al. Recommendations for participation in competitive sport and leisure-time physical activity in individuals with cardiomyopathies, myocarditis and pericarditis. *Eur J Cardiovasc Prev Rehabil*. 2006;13(6):876-885.

8. Maron BJ, Chaitman BR, Ackerman MJ, et al; Working Groups of the American Heart Association Committee on Exercise, Cardiac Rehabilitation, and Prevention; Councils on Clinical Cardiology and Cardiovascular Disease in the Young. Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases. *Circulation*. 2004;109(22):2807-2816.

9. 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(7):1034-1039.

10. Kokkinos P, Myers J, Kokkinos JP, et al. Exercise capacity and mortality in black and white men. *Circulation*. 2008;117(5):614-622.

11. Paffenbarger RS Jr, Hyde RT, Wing AL, Lee IM, Jung DL, Kampert JB. The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. *N Engl J Med*. 1993;328(8):538-545.

12. Sattelmair J, Pertman J, Ding EL, Kohl HW III, Haskell W, Lee IM. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. *Circulation*. 2011;124(7):789-795.

13. Sofi F, Capalbo A, Cesari F, Abbate R, Gensini GF. Physical activity during leisure time and primary prevention of coronary heart disease: an updated meta-analysis of cohort studies. *Eur J Cardiovasc Prev Rehabil*. 2008;15(3):247-257.

14. Fletcher GF, Ades PA, Kligfield P, et al; American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology, Council on Nutrition, Physical Activity and Metabolism, Council on Cardiovascular and Stroke Nursing, and Council on Epidemiology and Prevention. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation*. 2013;128(8):873-934.

15. O'Connor CM, Whellan DJ, Lee KL, et al; HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009;301(14):1439-1450.

16. Pandey A, Parashar A, Kumbhani DJ, et al. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. *Circ Heart Fail*. 2015;8(1):33-40.

17. Sharma S, Firoozi S, McKenna WJ. Value of exercise testing in assessing clinical state and prognosis in hypertrophic cardiomyopathy. *Cardiol Rev*. 2001;9(2):70-76.

18. Huff CM, Turer AT, Wang A. Correlations between physician-perceived functional status, patient-perceived health status, and cardiopulmonary exercise results in hypertrophic cardiomyopathy. *Qual Life Res*. 2013;22(3):647-652.

19. Scott NW, McPherson GC, Ramsay CR, Campbell MK. The method of minimization for allocation to clinical trials: a review. *Control Clin Trials*. 2002;23(6):662-674.

20. Olivotto I, Maron BJ, Montereggi A, Mazzuoli F, Dolara A, Cecchi F. Prognostic value of systemic blood pressure response during exercise in a community-based patient population with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 1999;33(7):2044-2051.

21. Sadoul N, Prasad K, Elliott PM, Bannerjee S, Frenneaux MP, McKenna WJ. Prospective prognostic assessment of blood pressure response during exercise in patients with hypertrophic cardiomyopathy. *Circulation*. 1997;96(9):2987-2991.

22. Borg GAV. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc*. 1982;14(5):377-381.

23. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc*. 2011;43(8):1575-1581.

24. Le VV, Perez MV, Wheeler MT, Myers J, Schnittger I, Ashley EA. Mechanisms of exercise intolerance in patients with hypertrophic cardiomyopathy. *Am Heart J*. 2009;158(3):e27-e34.

25. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation*. 1999;99(9):1173-1182.

26. Coats AJ, Adamopoulos S, Radaelli A, et al. Controlled trial of physical training in chronic heart failure. Exercise performance, hemodynamics, ventilation, and autonomic function. *Circulation*. 1992;85(6):2119-2131.

27. Hambrecht R, Niebauer J, Fiehn E, et al. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. *J Am Coll Cardiol*. 1995;25(6):1239-1249.

28. Vromen T, Kraal JJ, Kuiper J, Spee RF, Peek N, Kemps HM. The influence of training characteristics on the effect of aerobic exercise training in patients with chronic heart failure: a meta-regression analysis. *Int J Cardiol*. 2016;208:120-127.

29. Swank AM, Horton J, Fleg JL, et al; HF-ACTION Investigators. Modest increase in peak VO_2 is related to better clinical outcomes in chronic heart failure patients: results from heart failure and a controlled trial to investigate outcomes of exercise training. *Circ Heart Fail*. 2012;5(5):579-585.

30. Wen CP, Wai JP, Tsai MK, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet*. 2011;378(9798):1244-1253.

31. Sweeting J, Ingles J, Ball K, Semsarian C. Challenges of exercise recommendations and sports participation in genetic heart disease patients. *Circ Cardiovasc Genet*. 2015;8(1):178-186.

32. Klempfner R, Kamerman T, Schwammenthal E, et al. Efficacy of exercise training in symptomatic patients with hypertrophic cardiomyopathy: results of a structured exercise training program in a cardiac rehabilitation center. *Eur J Prev Cardiol*. 2015;22(1):13-19.

33. Coats CJ, Rantell K, Bartnik A, et al. Cardiopulmonary exercise testing and prognosis in hypertrophic cardiomyopathy. *Circ Heart Fail*. 2015;8(6):1022-1031.

34. Finocchiaro G, Haddad F, Knowles JW, et al. Cardiopulmonary responses and prognosis in hypertrophic cardiomyopathy: a potential role for comprehensive noninvasive hemodynamic assessment. *JACC Heart Fail*. 2015;3(5):408-418.

35. Sorajja P, Allison T, Hayes C, Nishimura RA, Lam CS, Ommen SR. Prognostic utility of metabolic exercise testing in minimally symptomatic patients with obstructive hypertrophic cardiomyopathy. *Am J Cardiol*. 2012;109(10):1494-1498.

36. Chan RH, Maron BJ, Olivotto I, et al. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. *Circulation*. 2014;130(6):484-495.