MEDICAL SCHOOL
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Stanford MEDICINE

The Randomized Exploratory Study of Exercise Training in Hypertrophic Cardiomyopathy

RESET-HCM

Sara Saberi, MD, MS

Background: Current exercise guidelines are controversial

- No data to inform recreational exercise recommendations
- US and European guidelines do not agree on safety of moderate intensity exercise[1,2]
- Concern: Does exercise trigger ventricular arrhythmias?
- In clinical practice, patients with HCM are often discouraged from participating in physical activity
  - Patients with HCM are less active than the general U.S. population[3]
  - 60% believe exercise restrictions negatively impact emotional well-being

1. Maron BJ et al. Circulation. 2004;109:2807-16.
2. Pelliccia A. et al. Eur J Cardiovasc Prev Rehabil. 2006;13:876-885.
3. Reineck E. et all. Am J Cardiol. 213;111:1034-39

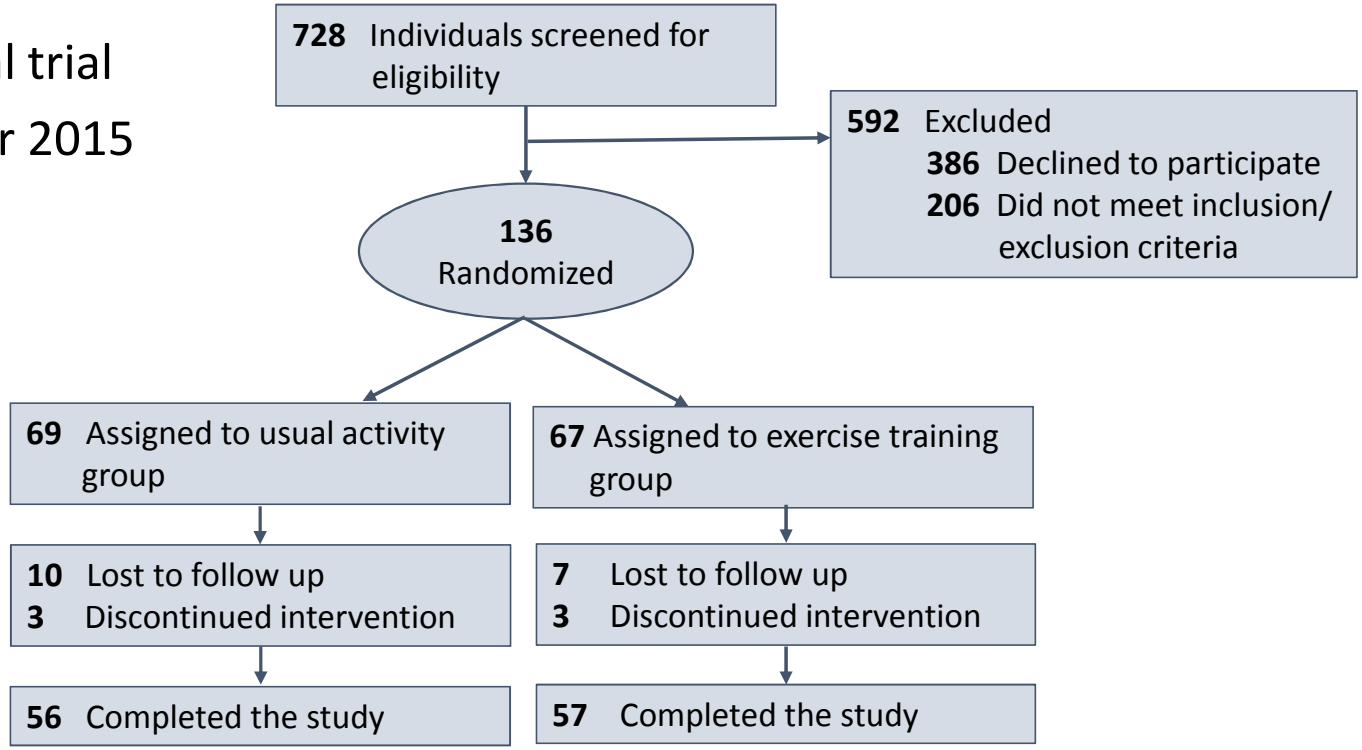
Objective

In patients with HCM, can moderate-intensity aerobic training improve exercise capacity without causing harm?

Methods: Design, Setting and Participants

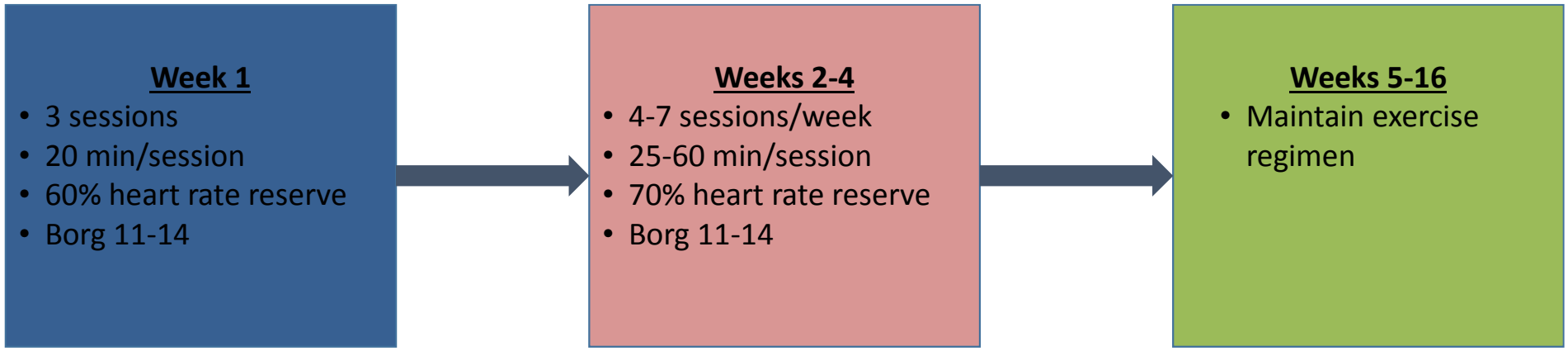
Randomized clinical trial

April 2010 – October 2015



Methods: Design, Setting and Participants

- Usual Activity: No exercise guidance
- Exercise Training:
  - Structured, home-based exercise program individually prescribed based on baseline heart rate reserve derived from baseline CPET
  - Recommended modes: walk-jog, cycling, elliptical

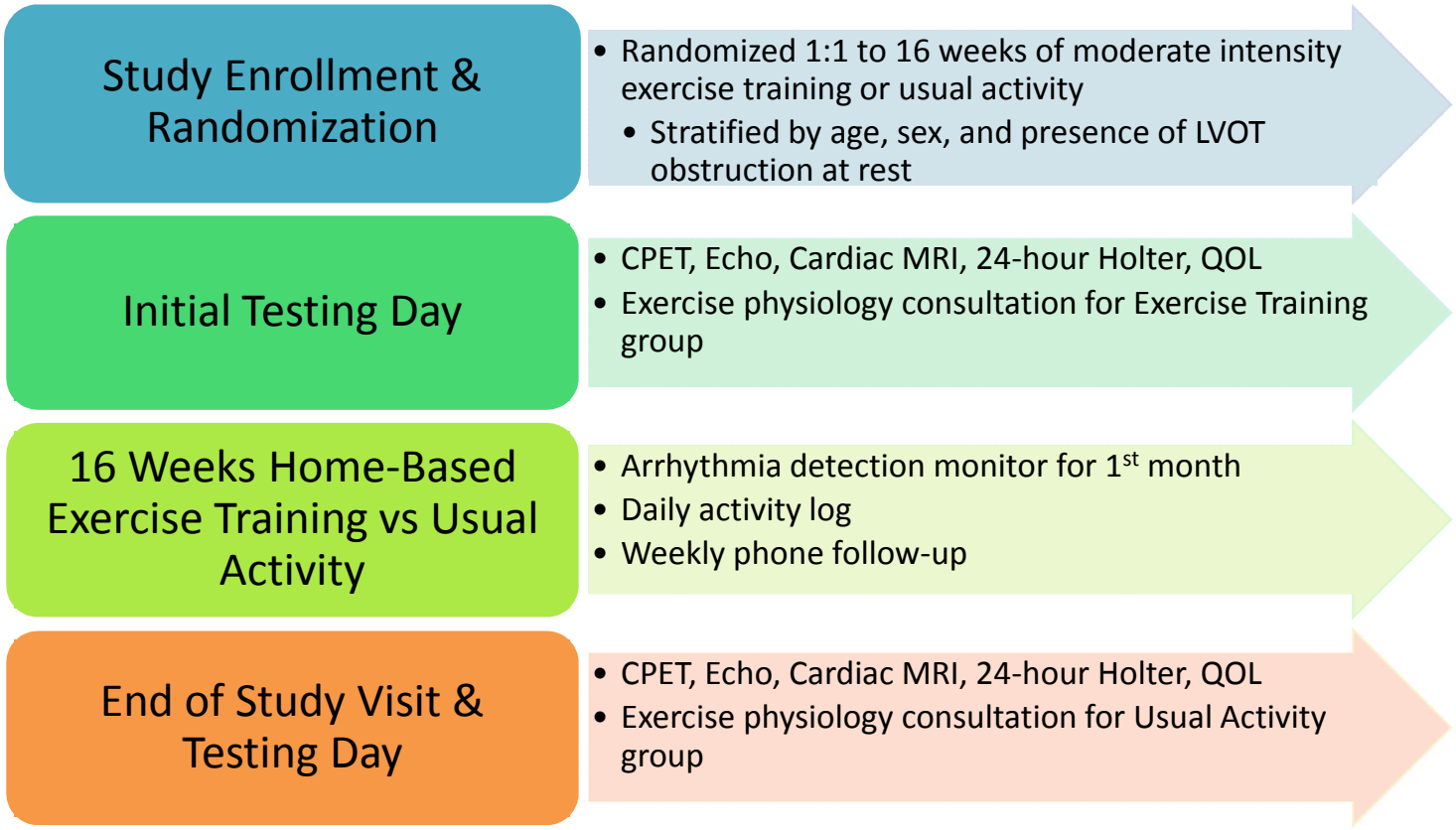


Methods: Inclusion/Exclusion Criteria

- **Inclusions**
  - HCM: presence of unexplained LVH ≥ 15 mm in any wall segment
  - 18-80 years old

- **Exclusions**
  - H/o exercise-associated ventricular arrhythmias/syncope
  - Hypotensive BP response (> 20 mm Hg drop in SBP) on prior exercise testing
  - EF < 55%
  - NYHA class IV
  - Unwilling to refrain from competitive sports

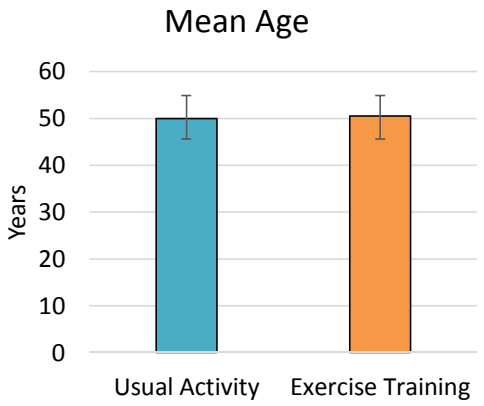
Methods: Intervention

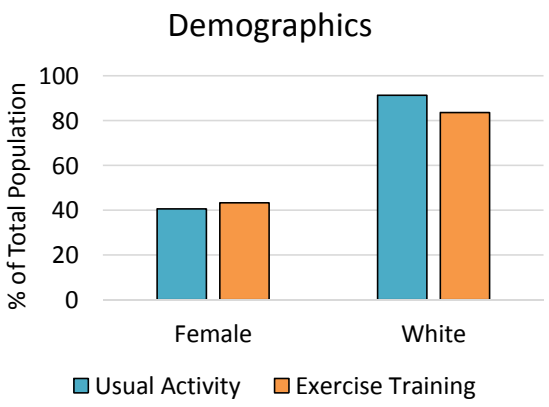


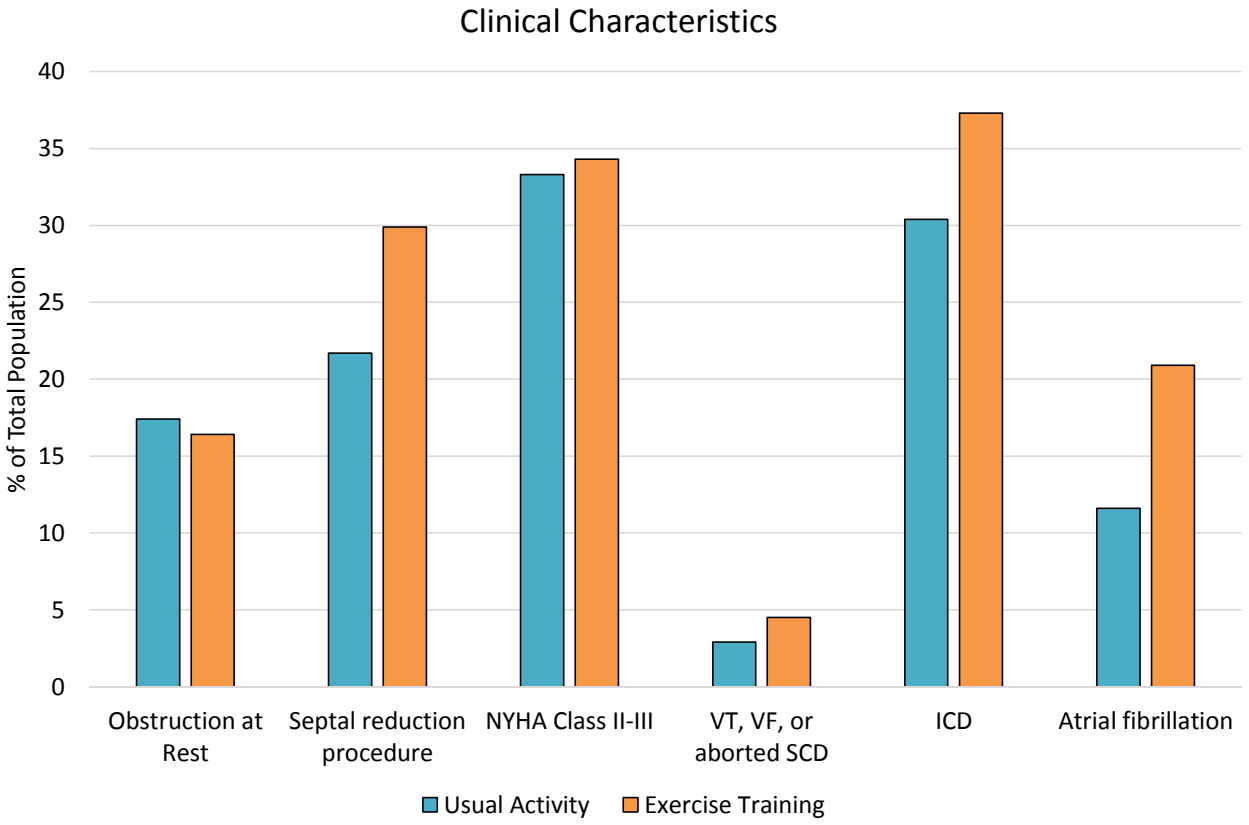
Methods: Outcomes

- **<u>Primary outcome measure:</u>**
  - Change in peak VO2 from baseline to 16 weeks
- **<u>Secondary outcomes:</u>**
  - Left ventricular hypertrophy and function
  - Scar volume on CMR
  - BNP
  - Degree of LVOT obstruction
  - Quality of life measures (SF-36v2, QIDS-SR_{16}, MLHF)
- **<u>Exploratory outcomes:</u>**
  - Other measures of exercise performance
  - Nonfatal arrhythmias
  - PVC burden

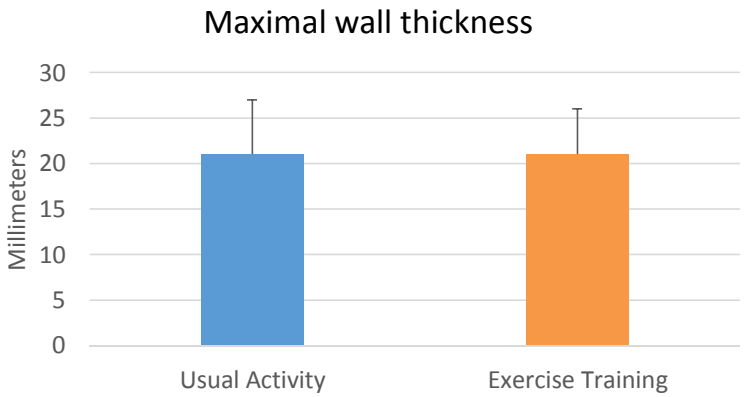
Results: Demographic and Clinical Characteristics at Baseline

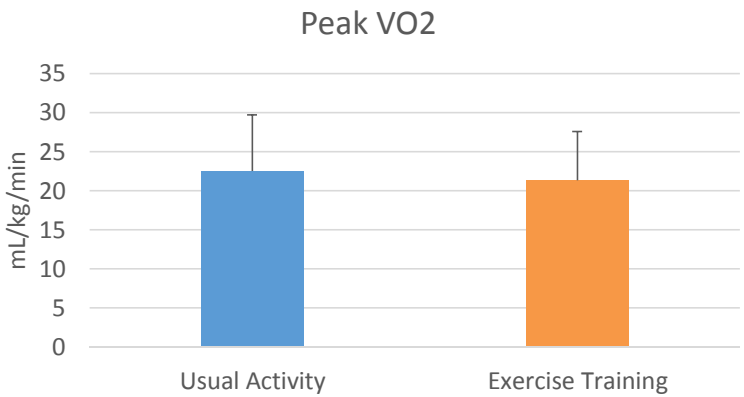




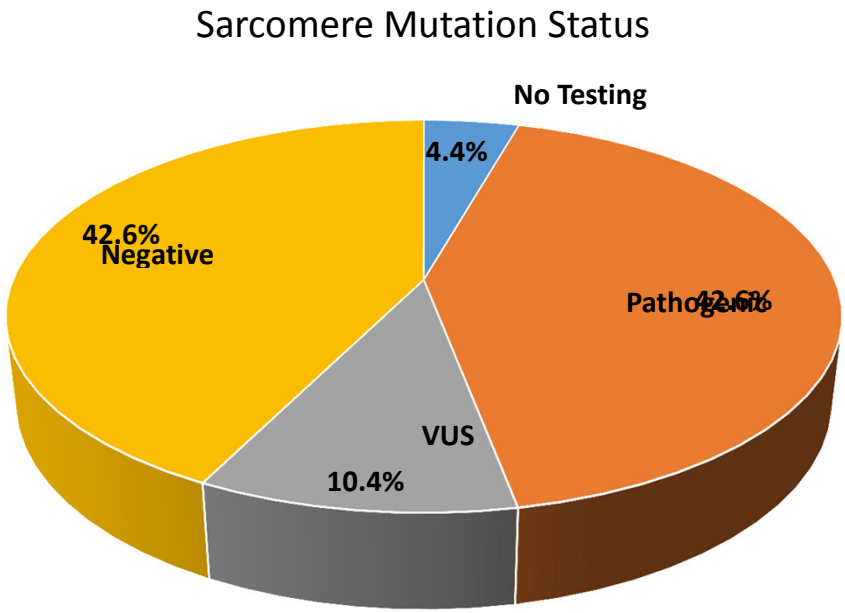


Results: Demographic and Clinical Characteristics at Baseline



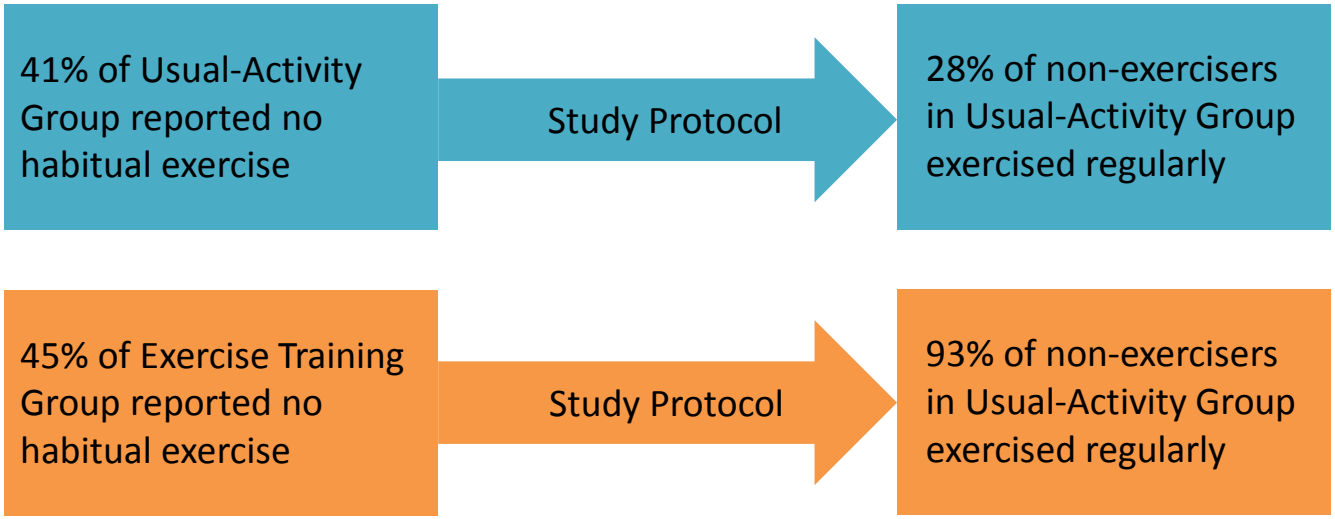


All but 1 of the patients who completed the study protocol underwent genetic testing.



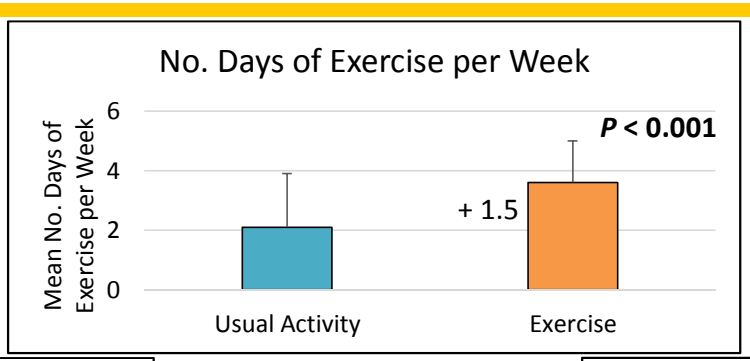
Results: Intervention Participation

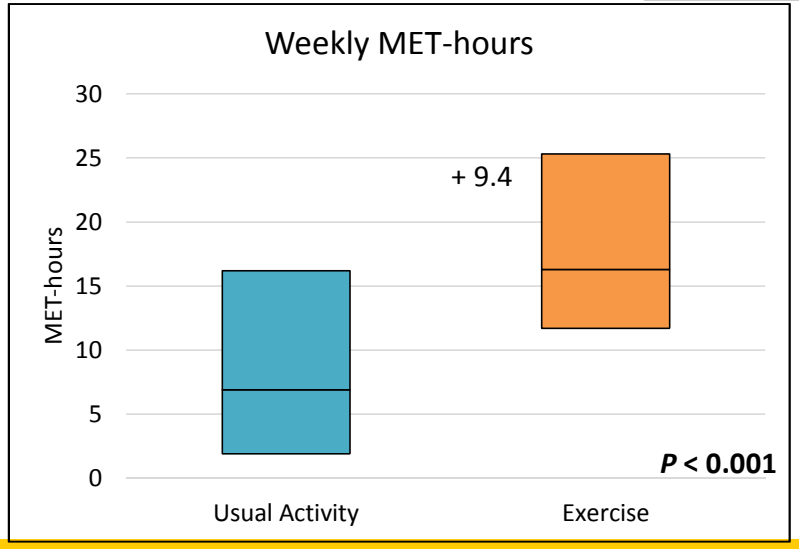
Prior to enrollment

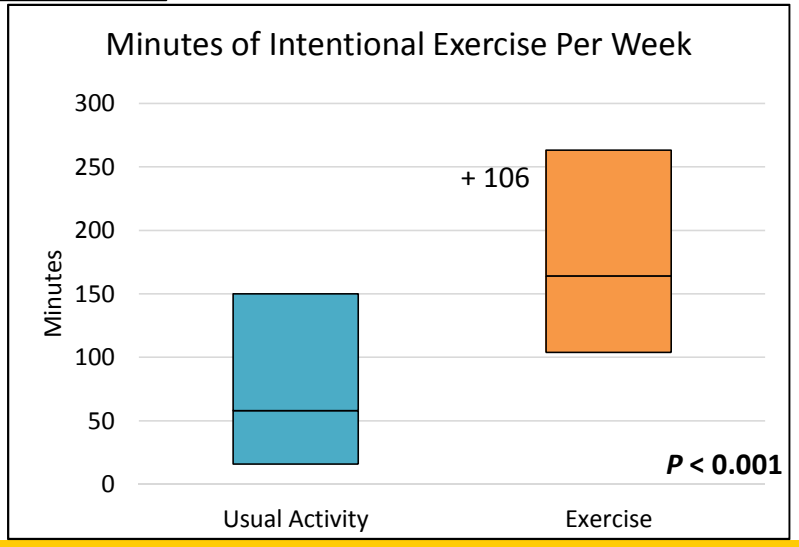


Most Common Modes of Exercise
Walking
Cycling
Jogging/Running
Elliptical
Aerobics
Stair Climbing

Results: Intervention Participation



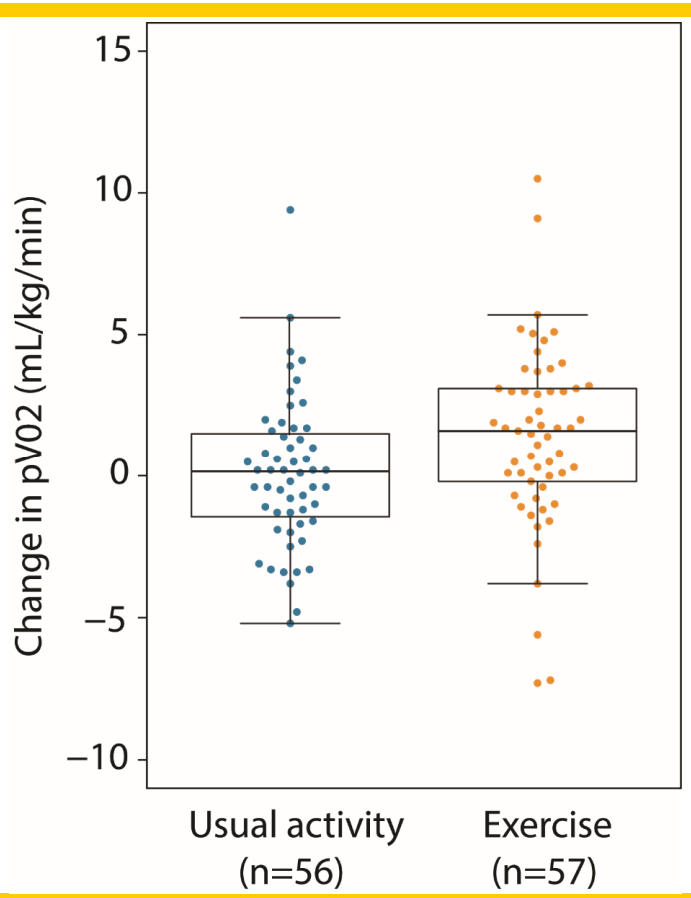




Results: Primary Endpoint
Change in peak VO2

Between Group Difference in Mean Change **1.27** mL/kg/min, ***P* = 0.02** (95% CI, 0.17 – 2.37)

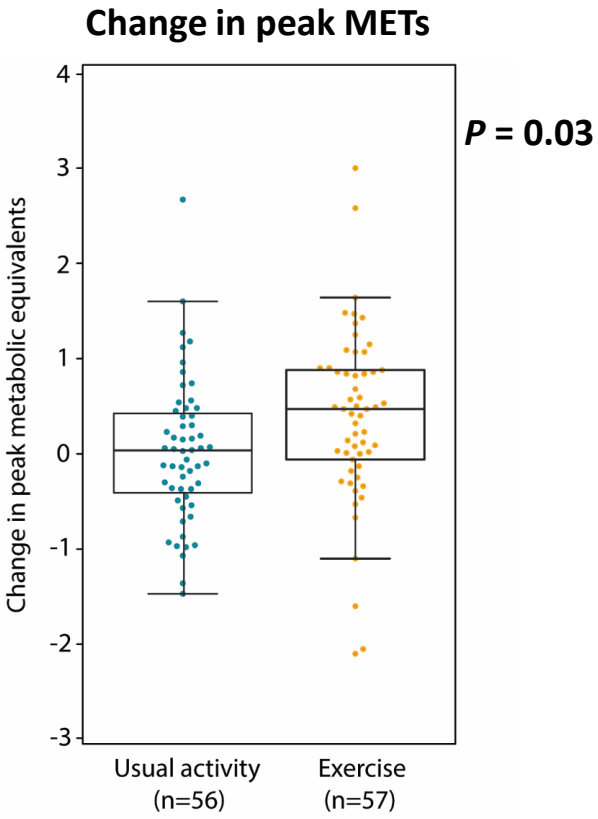
<u>Absolute increase in peak VO2 of 6%</u>

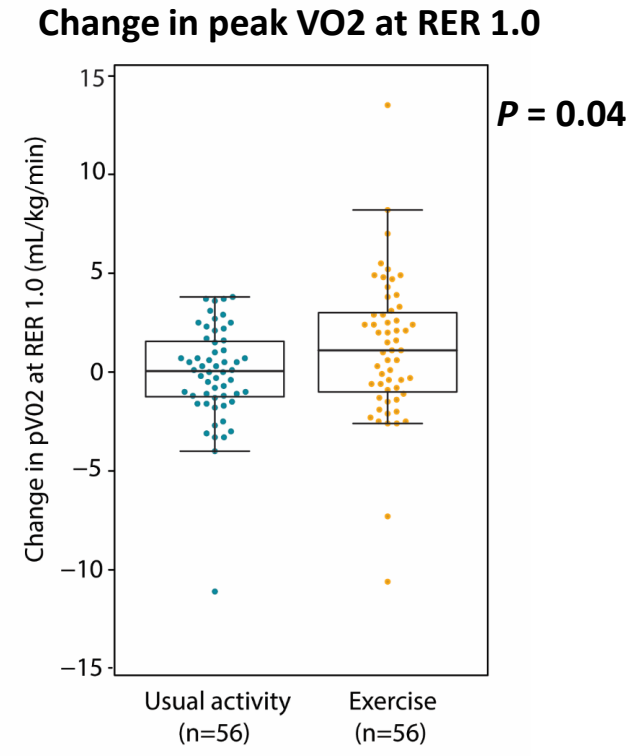


Adjusting for baseline peak VO2, genetic status and study site did not attenuate the difference in peak VO2.

Sensitivity analysis using multiple imputation including all 136 participants did not attenuate the effect.

Results: Exploratory Endpoints
Change in Other Exercise Capacity Measures





Results: Adverse Events

There were no occurrences of major adverse events, including death, aborted sudden cardiac death, appropriate ICD therapies, or sustained ventricular tachycardia in either group.

Variable	Usual Activity (n=69)	Exercise (n=67)
Nonsustained ventricular tachycardia, No. (%)	15 (23.1)	19 (31.7)
Atrial fibrillation, No. (%)	7 (11.5)	5 (8.8)
Supraventricular tachycardia, No. (%)	29 (47.5)	23 (40.3)
Syncope, No. (%)	2 (2.9)	0
Musculoskeletal injury, No. (%)	3 (4.3)	3 (4.5)

Results: Secondary and Exploratory Outcomes

- No significant changes in left ventricular hypertrophy or function, scar volume or BNP.

- Significant improvement in the Physical Functioning scale of SF-36v2 (between group difference 8.2, [95% CI 2.6 to 13.7]; *P* = 0.004).

- Significant reduction in PVC burden (between group difference from log-transformed data, -0.91 [95% CI, -1.76 to -0.05] PVC/h; *P* = 0.04).
  - Absolute between group difference -8.8 PVC/h

Limitations

1. Study was subject to potential sampling bias
2. Effect size of exercise training was relatively modest
3. No major adverse events and no signal for harm, but study not powered to assess safety
4. Not possible to blind patients to treatment assignment
5. Exercise prescription only incorporated moderate-intensity aerobic exercise in adult patients. This study does not address higher intensity recreational exercise or competitive sports participation.

Conclusions

- Moderate-intensity exercise compared with usual activity resulted in a significant increase in exercise capacity at 16 weeks – **absolute increase in peak VO2 of 6%**.
- No major adverse events.
- No difference between groups in nonfatal arrhythmias or cardiac remodeling.
- Improvements in secondary measures of exercise capacity, PVC burden and QOL in the exercise group.

Implications and Future Directions

- No clinical trial has previously implemented an exercise intervention in patients with HCM.

- Trial supports moderate-intensity exercise as an intervention for improving exercise capacity in patients with HCM.
  - HF-ACTION[4]: exercise intervention ⟶ absolute increase in peak VO2 of 0.6 mL/kg/min, or 4%.
  - HF-ACTION[5]: every 6% increase in peak VO2 ⟶ 8% lower risk for CV mortality or HF hospitalizations

- Future studies to address safety and benefits of more vigorous aerobic exercise, isometric activities, and **participation in competitive sports** in both adult and pediatric patients with HCM

- Future studies with longer follow-up to assess the clinical importance of these findings and any potential influence of exercise on disease progression

4. O'Connor CM et al. JAMA. 2009;301:1439-50.
5. Swank AM et al. Circ Heart Fail. 2012;5:579-85.

Research

JAMA | Preliminary Communication

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

A Randomized Clinical Trial

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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

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