The Randomized Exploratory Study of Exercise Training in Hypertrophic Cardiomyopathy

RESET-HCM

Sara Saberi, MD, MS
No data to inform recreational exercise recommendations

US and European guidelines do not agree on safety of moderate intensity exercise

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
  • 60% believe exercise restrictions negatively impact emotional well-being

References:
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?
Randomized clinical trial
April 2010 – October 2015

- **728** Individuals screened for eligibility
- **592** Excluded
  - **386** Declined to participate
  - **206** Did not meet inclusion/exclusion criteria

- **136** Randomized
  - **69** Assigned to usual activity group
    - **10** Lost to follow up
    - **3** Discontinued intervention
    - **56** Completed the study
  - **67** Assigned to exercise training group
    - **7** Lost to follow up
    - **3** Discontinued intervention
    - **57** Completed the study
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

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Weeks 2-4</th>
<th>Weeks 5-16</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 sessions</td>
<td>4-7 sessions/week</td>
<td>Maintain exercise regimen</td>
</tr>
<tr>
<td>20 min/session</td>
<td>25-60 min/session</td>
<td></td>
</tr>
<tr>
<td>60% heart rate reserve</td>
<td>70% heart rate reserve</td>
<td></td>
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<tr>
<td>Borg 11-14</td>
<td>Borg 11-14</td>
<td></td>
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</tbody>
</table>
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

Study Enrollment & Randomization
- Randomized 1:1 to 16 weeks of moderate intensity exercise training or usual activity
- Stratified by age, sex, and presence of LVOT obstruction at rest

Initial Testing Day
- CPET, Echo, Cardiac MRI, 24-hour Holter, QOL
- Exercise physiology consultation for Exercise Training group

16 Weeks Home-Based Exercise Training vs Usual Activity
- Arrhythmia detection monitor for 1st month
- Daily activity log
- Weekly phone follow-up

End of Study Visit & Testing Day
- CPET, Echo, Cardiac MRI, 24-hour Holter, QOL
- Exercise physiology consultation for Usual Activity group
Methods: Outcomes

• **Primary outcome measure:**
  • Change in peak VO2 from baseline to 16 weeks

• **Secondary outcomes:**
  • Left ventricular hypertrophy and function
  • Scar volume on CMR
  • BNP
  • Degree of LVOT obstruction
  • Quality of life measures (SF-36v2, QIDS-SR16, MLHF)

• **Exploratory outcomes:**
  • Other measures of exercise performance
  • Nonfatal arrhythmias
  • PVC burden
Results: Demographic and Clinical Characteristics at Baseline

### Demographics

#### Mean Age

- **Usual Activity**: [Mean age bar chart]
- **Exercise Training**: [Mean age bar chart]

#### Female and White Population

- **Female**: [Bar chart]
- **White**: [Bar chart]

### Clinical Characteristics

- **Obstruction at Rest**: [Bar chart]
- **Septal reduction procedure**: [Bar chart]
- **NYHA Class II-III**: [Bar chart]
- **VT, VF, or aborted SCD**: [Bar chart]
- **ICD**: [Bar chart]
- **Atrial fibrillation**: [Bar chart]

**Legend**

- **Usual Activity**
- **Exercise Training**
All but 1 of the patients who completed the study protocol underwent genetic testing.

**Maximal wall thickness**

- Usual Activity: 22 mm
- Exercise Training: 25 mm

**Peak VO2**

- Usual Activity: 28 mL/kg/min
- Exercise Training: 25 mL/kg/min

**Sarcomere Mutation Status**

- Pathogenic: 42.6%
- VUS: 10.4%
- No Testing: 4.4%
Prior to enrollment

41% of Usual-Activity Group reported no habitual exercise

Study Protocol

28% of non-exercisers in Usual-Activity Group exercised regularly

45% of Exercise Training Group reported no habitual exercise

Study Protocol

93% of non-exercisers in Usual-Activity Group exercised regularly

Most Common Modes of Exercise
Walking
Cycling
Jogging/Running
Elliptical
Aerobics
Stair Climbing
Results: Intervention Participation

No. Days of Exercise per Week

<table>
<thead>
<tr>
<th>Days of Exercise per Week</th>
<th>Usual Activity</th>
<th>Exercise</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>+1.5</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
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</table>

Weekly MET-hours

<table>
<thead>
<tr>
<th>MET-hours</th>
<th>Usual Activity</th>
<th>Exercise</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td></td>
<td>+9.4</td>
<td>&lt; 0.001</td>
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Minutes of Intentional Exercise Per Week

<table>
<thead>
<tr>
<th>Minutes</th>
<th>Usual Activity</th>
<th>Exercise</th>
<th>P</th>
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<tbody>
<tr>
<td>100</td>
<td></td>
<td>+106</td>
<td>&lt; 0.001</td>
</tr>
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</table>
Between Group Difference in Mean Change 1.27 mL/kg/min, \( P = 0.02 \) (95% CI, 0.17 – 2.37)

Absolute increase in peak VO2 of 6%

Results: Primary Endpoint
Change in peak VO2

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

**Change in peak METs**
- Usual activity (n=56)
- Exercise (n=57)

\[ P = 0.03 \]

**Change in peak VO2 at RER 1.0**
- Usual activity (n=56)
- Exercise (n=56)

\[ P = 0.04 \]
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.

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<thead>
<tr>
<th>Variable</th>
<th>Usual Activity (n=69)</th>
<th>Exercise (n=67)</th>
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<tbody>
<tr>
<td>Nonsustained ventricular tachycardia, No. (%)</td>
<td>15 (23.1)</td>
<td>19 (31.7)</td>
</tr>
<tr>
<td>Atrial fibrillation, No. (%)</td>
<td>7 (11.5)</td>
<td>5 (8.8)</td>
</tr>
<tr>
<td>Supraventricular tachycardia, No. (%)</td>
<td>29 (47.5)</td>
<td>23 (40.3)</td>
</tr>
<tr>
<td>Syncope, No. (%)</td>
<td>2 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal injury, No. (%)</td>
<td>3 (4.3)</td>
<td>3 (4.5)</td>
</tr>
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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\textsuperscript{4}: exercise intervention \(\rightarrow\) absolute increase in peak VO\textsubscript{2} of 0.6 mL/kg/min, or 4%.
  - HF-ACTION\textsuperscript{5}: every 6% increase in peak VO\textsubscript{2} \(\rightarrow\) 8% lower risk for CV mortality or HF hospitalizations

- Future studies to address safety and benefits of more vigorous aerobic exercise, isometric activities, and \textbf{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

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

S Saberi et al.

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