Camino de Santiago
Exercise Testing in FH Exercise Testing Guidelines for Patients with Familial Hypercholesterolemia

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Disclosure

AstraZeneca – Speakers Bureau
Discussion Topics

Utility of serial graded exercise testing (GXT) in FH

Prevalence of positive GXT ECG’s in FH

LDL-C and Apo B reduction and GXT ECG changes

Improving GXT administration and interpretation in FH
The Utility of Exercise Tolerance Testing in Outpatient Lipid Clinics in 2014
Lovelace Clinic, Preventive Cardiology/Aerospace Medicine Division
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17,000 GXT’s 1973-77
The Value of Clinical/Functional Exercise Capacity Assessment in FH

- Comparative myocardial ischemic thresholds pre/post statin, apheresis and/or lifestyle therapy
- Predictive power: MET capacity, BP, ECG eval, S-T/HR slope, recovery parameters
- Exercise generated ventricular dysrhythmia evaluation
- Chronotropic response
- Exercise training risk evaluation
- Functional capacity (MET capacity)
- Motivational tool
Key Points:

- Exercise ECG testing can be helpful in determining *serial* ischemic response to exercise in FH

- Exercise testing can evaluate exercise-related CV complications, eg. ex ventricular dysrhythmias

- Exercise testing is motivational to patients perception of fitness and functional capacity
University of Athens
Exercise capacity and heart rate recovery as predictors of CHD events, in patients with heterozygous Familial Hypercholesterolemia.

639 cardiovascular disease-free patients with heterozygous FH; End point: fatal or non-fatal CHD.

**RESULTS:** 15 yr f/u: 53 (18%) men and 34 (10%) women developed a CHD event (11 were fatal).

**Predictors of CHD events:**

- **Exercise capacity** (hazard ratio = 0.82, P < 0.001),
- Heart rate recovery at 1 min (hazard ratio = 0.91, P < 0.05),
- Peak pulse pressure levels (hazard ratio = 1.03, P < 0.001),

We evaluated 62 GXT’s in equal numbers of heterozygous for familial hypercholesterolemia (hFH) and healthy (HLY) women, matched for age, baseline systolic and diastolic blood pressure and baseline heart rate, using the Bruce protocol.

Women with hFH had lower delta (difference of peak to baseline) and peak exercise systolic and diastolic BP (systolic: 167 mmHg vs. 177 mmHg and DPB 48 vs. 58mmHg, p=0.010 and p=0.042, respectively)

✔ hFH women possibly have an inadequate rise in systolic BP

Apheresis Atherosclerosis Regression Study (LAARS)

N=42 heFH men, 2 years

Apheresis vs Simvastatin Rx

Apheresis:
63% LDL red.
49% ApoB red.

✔️ Time to 0.1 mv S-T dep. incr. 39%
Max S-T depress. decre
No change in simva group

p= 0.001

Reduction of exercise-induced ST segment depression following long-term serum lipid lowering by drugs in hyperlipoproteinemia

Anders G. Olsson, Lars-Göran Ekelund  Atherosclerosis 1983;47:297

- N=34 asymptomatic hypercholesterolemic adults
- 70% positive exercise ischemic responses

Statin Rx for 5 years increased time to abnormal exercise S-T changes
Intensive vs. Moderate LDL Lowering and Exercise ECG Ischemic Response

• 300 patients with stable CAD, a positive exercise treadmill test, 48-hour ambulatory ECG

• 1-year treatment with intensive atorvastatin or diet and low-dose

• LDL-C 153 to 83 mg/dL Atorva
  147 to 120 mg/dL D+ Lova

✓ Mean exercise duration to 1-mm ST-segment depression significantly increased in each group (moderate or intensive statin Rx)

Stone PH, Lloyd-Jones DM et.al. Circ. 2005 111:1747
Cholesterol lowering with statins reduces exercise-induced myocardial ischemia in heFH patients with CAD

FH patients were randomly assigned to a 16-week treatment period with either diet alone (n = 39) or diet plus statins (simvastatin, n = 31 and pravastatin, n = 10). All with positive ETT

✔ After 16 weeks

36 patients (92%) in the diet group still had positive exercise tests

7 patients (15%) of the statin + d group had a positive test (p <0.01).

► The proportion of positive tests was significantly reduced in subgroups of patients with 1-, 2-, or 3-vessel disease.

► Regarding the severity of coronary stenosis, the proportion of positive tests was significantly reduced in patients with stenosis between 70% and 90%
Silent ischaemia in familial hypercholesterolemia.

In a cohort of 66 FH-men (age 25-55) prospectively recruited during a 2-years period, we estimated the incidence of coronary heart disease to 52% (N=34).

32% (N=21) had earlier history of symptomatic ischaemic disease

20% (N=13) had significant ST/T changes during exercise stress test.

Amongst the 8 patients with positive exercise stress test who underwent coronary angiography, six had severe coronary artery disease.

Because of the severity of the stenotic lesions, 4 of these 6 patients underwent coronary angioplasty or surgical bypass.

We concluded that a great proportion of FH men suffered from myocardial ischaemia, either asymptomatic or symptomatic, and that even the silent form is associated with severe coronary stenosis.

This advocates to systematically perform exercise testing in asymptomatic FH men after age 25.
Key points:

• Diminished exercise tolerance, decreased HR response, increased peak pulse pressure, and slower heart rate recovery, and abnormal ischemic electrocardiographic responses in FH patients

• Exercise time to ECG ischemic response is a helpful outcome measure of improved functional capacity and increases ischemic threshold

• LDL lowering therapy with apheresis or statins can reduce exercise-generated myocardial ischemia (time to abnormal S-T changes)
The cases of two brothers training and competing as master cyclists and both preparing for a cycling tour are presented.

Both brothers had heterozygous FH.

The older brother aged 66 years went first to the primary care physician and presented with asymptomatic s-t depression in V5 and V6 during the final stages of the exercise test and in recovery after complete exhaustion.

Coronary angiography revealed a multi vessel coronary artery disease and he underwent bypass surgery.
One year later, he successfully completed his planned cycling tour of 373 miles (600 km) in seven stages and covering ~12,000 m of total ascent.

The younger brother aged 59 years went a few months later to the primary care physician and also performed asymptomatic exercise stress testing without changes in the ST segments.

He suffered a cardiac arrest 2 months later during a cycling tour and was successfully resuscitated. CT angiography showed 3 ves. Dis.

Rüst et. al. 2013
Key point:

Abnormal prognostic exercise responses extend beyond ECG S-T abnormalities.

- Very low exercise tolerance (<6 MET’s)
- Blunted heart rate response
- Inadequate BP response to increasing work load
- Exercise generated ventricular dysrhythmias
Multifocal ventricular ectopic beats (ex recovery)

LBMC 1976 cc
Exercise-induced non-sustained ventricular tachycardia
During near peak exercise

✓ NSVT + FH = further workup (e.g. structural abnormalities)
Characterizing differences in mortality at the low end of the fitness spectrum in individuals with cardiovascular disease

- A total of 5101 patients with a history of CVD underwent clinical treadmill testing and were followed up for 9.1+/−5.5 years
- Patients were classified into quintiles of exercise capacity measured in metabolic equivalents.

FIGURE 2—Kaplan-Meier curves for all-cause mortality across quintiles of fitness in healthy individuals. Quintile 1, least-fit; quintile 5, most-fit.
Kodama et al. (JAMA, 2009) performed a meta-analysis that collectively included 33 studies totaling more than 100,000 subjects and 6,000 all-cause mortality and 4,000 cardiovascular events.

They found estimated aerobic capacity from treadmill speed and grade or ergometer workload was a consistent prognostic marker in apparently healthy men and women.

✔️ Each 1 MET increase in aerobic capacity reflected a 13% decrease in all-cause mortality and 15% decrease in cardiovascular events.
The prognostic value of exercise capacity: a review of the literature

< 6 MET’s had higher CVD mortality

>10 MET’s relative protective effect
Key point:

Low CRF (inadequate MET response, eg. <6 MET’s*) is prognostic of moderate and long term CV outcomes.

There is no reason to believe that this would be different in FH patients

* e.g., 3.0 mph/7.5% grade = 6 METs
ACSM’s Guidelines for Exercise Testing and Prescription

NINTH EDITION
Performing Quality GXT’s in Cardiology

1. Test protocol should be individualized so that the treadmill speed and increments in grade are **based on the subject’s perceived functional capacity**.

   Ideally, increments in work rate should be chosen so that the total test time ranges between **10 and 15 min**, assuming the endpoint is volitional max.

2. Blood pressure measurement every stage of the GXT

3. ≥ 85% of HR max

4. Recovery for 10+ minutes

5. Test outcome parameters: **HR % BP response, ventricular rhythm, S-T and S-T – HR slope changes, exertional symptoms/signs, MET’s or work achieved.**
Balke TM Protocol

Self-selected speed (then kept constant)

2.0, 2.5, 3.0, 3.5, 4.0 mph

Graduated increase in % grade

1% per minute

or

2.5% grade every two minutes
MET REQUIREMENTS
Bruce Protocol
Purpose of this Website
This site is designed to provide the updated 2011 Compendium of Physical Activities and additional resources. The 2011 update identifies and updates MET codes that have published evidence to support the values. In addition, new codes have been added to reflect the growing body of knowledge and popular activities.

Website Search Tips: Enter keywords into the search box found on the upper right hand corner of the page. This will search and return results from the entire site including PDF files. Oftentimes keywords are found on multiple pages (e.g., tractor can be found on Lawn & Garden, Occupation, and Transportation). Once you have selected a specific page, use CTRL + F to bring up another search box that will search the entered keyword only on that page.

History
The Compendium of Physical Activities was developed for use in epidemiologic studies to standardize the assignment of MET intensities in physical activity questionnaires. Dr. Bill Haskell from Stanford University conceptualized the Compendium and developed a prototype for the document. The Compendium was used first in the Survey of Activity, Fitness, and Exercise (SAFE study - 1987 to 1989) to code and score physical activity records. Since then, the Compendium has been used in studies worldwide to assign intensity units to physical activity questionnaires and to develop innovative ways to assess energy expenditure in physical activity studies. Version 1 of the Compendium was published in 1993. An updated version was published in 2000. References for the publications are below.

Definition of Terms used in the Compendium
MET (Metabolic Equivalent): The ratio of the work metabolic rate to the resting metabolic rate. One MET is defined as 1 kcal/kg/hour and is roughly equivalent to the energy cost of sitting quietly. A MET also is defined as oxygen uptake in ml/kg/min with one MET equal to the oxygen cost of sitting quietly, equivalent to 3.5 ml/kg/min.

5-Digit Code: Compendium activities are classified by a 5-digit code that identifies the category (heading) as the first 2 digits and type (description) of activity as the last three digits. Example:

<table>
<thead>
<tr>
<th>Code</th>
<th>Heading</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>03010</td>
<td>01</td>
<td>Bicycling</td>
</tr>
<tr>
<td>010</td>
<td>01</td>
<td>Bicycling, &lt; 10 mph, bicycling to work or for pleasure (Taylor code 115)</td>
</tr>
</tbody>
</table>
**TABLE 2. Major types of physical activities in the 2011 Compendium.**

<table>
<thead>
<tr>
<th>No.</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bicycling</td>
</tr>
<tr>
<td>2</td>
<td>Conditioning exercises</td>
</tr>
<tr>
<td>3</td>
<td>Dancing</td>
</tr>
<tr>
<td>4</td>
<td>Fishing and hunting</td>
</tr>
<tr>
<td>5</td>
<td>Home activity</td>
</tr>
<tr>
<td>6</td>
<td>Home repair</td>
</tr>
<tr>
<td>7</td>
<td>Inactivity</td>
</tr>
<tr>
<td>8</td>
<td>Lawn and garden</td>
</tr>
<tr>
<td>9</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>10</td>
<td>Music playing</td>
</tr>
<tr>
<td>11</td>
<td>Occupation</td>
</tr>
<tr>
<td>12</td>
<td>Running</td>
</tr>
<tr>
<td>13</td>
<td>Self-care</td>
</tr>
<tr>
<td>14</td>
<td>Sexual activity</td>
</tr>
<tr>
<td>15</td>
<td>Sports</td>
</tr>
<tr>
<td>16</td>
<td>Transportation</td>
</tr>
<tr>
<td>17</td>
<td>Walking</td>
</tr>
<tr>
<td>18</td>
<td>Water activities</td>
</tr>
<tr>
<td>19</td>
<td>Winter activities</td>
</tr>
<tr>
<td>21</td>
<td>Religious activities</td>
</tr>
<tr>
<td>21</td>
<td>Volunteer activities</td>
</tr>
</tbody>
</table>

ECG interpretation is only paid when performed by a physician. In addition, the ordering physician must be identified on any claim from a laboratory or other setting at which the ECG services were furnished.

Since Medicare does not cover screening ECG tests for routine examinations, claims should indicate signs, symptoms, appropriate reason codes, or other clinical justification for the services.
✓ “Functional Myocardial Ischemic Exercise Tolerance Threshold in FH”
Key points:

The value of clinical/functional exercise capacity assessment in FH

- Comparative myocardial ischemic thresholds
- Predictive power e.g., MET capacity, HR response
- Exercise generated ventricular dysrhythmia evaluation
- Exercise training risk evaluation (ex generated CV compl)
- Functional capacity
- Motivational tool