Stress Testing in the Cardiac Patient: What’s the Best Way

Dr. Alain Bouchard
Chronic Ischemic Heart Disease

Epidemiology

• 17 million Americans have CAD
• 10 million Americans have angina
• Age 60-79 – 25% of men, 16% of women
• Age $\geq$80-37% of men, 23% of women

Clinical Classification of Chest Pain

Typical angina:  
(definite)  
1) Substernal chest discomfort with a characteristic quality and duration that 
2) provoked by exertion or emotional stress 
3) relieved by rest or nitroglycerin

Atypical angina:  
(probable)  
Meets 2 of the above characteristics

Noncardiac pain:  
Meets 1 or none of the typical anginal chest characteristics

Grading Angina Pectoris: Canadian Cardiovascular Society Classification

Class I: Ordinary activity → no angina
  - Walking, climbing stairs

Class II: “Slight limitation”
  - Walking rapidly
  - Activity after meal
  - Walk in cold, wind, AM
  - Climb stairs fast
  Can: walk 2 blocks or one flight of stairs without angina.

Class III: “Marked limitations”
  - Walking 1-2 blocks
  - Climb 1 flight of stairs

Class IV: “Unstable”
  - Any activity
  - Pain at rest

JACC 2003;41:158-68.
Atherothrombosis
A Generalized and Progressive Process

Adapted from Libby P
The Ischemic Cascade

Progressive Manifestations of Ischemia

- Repolarization/ECG Changes
- Global Systolic Dysfunction
- Regional Wall Motion
- ↓ Epicardial Perfusion
- Diastolic Dysfunction
- Altered Metabolism
- ↓ Subendocardial Perfusion
- Vascular Dysfunction

Exposure Time of Mismatch in Myocardial Oxygen Supply/Demand

Near Term → Prolonged

Spectrum of IHD

Noninvasive Testing

Asymptomatic (SIHD)

Features of Low-Risk Unstable Angina:
- Age <70y
- Exertional Pain Lasting <20min
- Pain not Rapidly Accelerating
- Normal or Unchanged ECG
- No Elevation of Cardiac Markers

Stable Angina or Low-Risk UA (SIHD; PCI/CABG)

Acute Coronary Syndromes (UA/NSTEMI; STEMI; PCI/CABG)

New Onset Chest Pain (SIHD; UA/NSTEMI; STEMI)

Noncardiac Chest Pain

Sudden Cardiac Death (VA-SCD)

Patients with Known IHD

Asymptomatic (SIHD)

Persons without Known IHD

Asymptomatic

Known IHD (CV Risk)

Diagnosis of Patients with Suspected Ischemic Heart Disease

Suspected Ischemic Heart Disease
(or change in clinical status in a patient with known IHD)

See ACCF/AHA UA/NSTEMI Guideline

Intermediate or High-Risk UA?

No

Symptoms or findings suggest high-risk lesion(s)
OR
Prior sudden death or serious ventricular arrhythmia
OR
Prior stent in unprotected left main coronary artery

Comprehensive clinical assessment of risk, including personal characteristics, coexisting cardiac and medical conditions, and health status

Yes

Recent Exercise or Cardiac Imaging Study

No

Diagnosis of Patients with Suspected Ischemic Heart Disease

Recent Exercise or Cardiac Imaging Study

Contraindications to Stress Testing?

Patient Able to Exercise?

Previous Coronary Revascularization? 

Resting ECG Interpretable?

MPI or Echo w/ Exercise

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No
Diagnosis of Patients with Suspected Ischemic Heart Disease

1. **Technically Adequate?**
   - Yes
     - Low Likelihood IHD
     - Intermediate to High Likelihood IHD
     - **OR**
       - Pharm Stress Echo
       - Pharm CMR or CCTA
       - Pharm Stress MPI or Echo
   - No
     - Pt. able to Exercise? Prev. Coronary Revasc.?
     - No
       - Resting ECG Interpretable?
         - Yes
           - **OR**
             - Low Likelihood IHD
             - Intermediate Likelihood IHD
             - Intermediate to High Likelihood IHD
       - No
         - **MPI or Echo w/ Exercise or Pharm CMR**
         - CCTA
   - Yes
     - **Test Results Suggest High-Risk Coronary Lesion(s)?**
       - No
         - **Initiate Guideline-Directed Medical Therapy**
       - Yes
         - Go to Figure 4

NonInvasive Risk Stratification

Low Risk: <1% Annual MI or Death

- CAC Score <100 Agaston Units
- Normal or Small Perfusion Defect at Rest or with Stress <5% of Heart
- No Change of Limited WMA on Stress
- No Coronary Stenosis >50% on CTA
- No Ischemic Sx on Maximum ETT
- No Ischemia ECG Δ’s on Maximum ETT
- No Stress Induced WMA
NonInvasive Risk Stratification

Interm. Risk: 1-3% Annual MI or Death

- LVEF: 35-49%
  - WMA ≤2 Segments and 1 Coronary Area
- 1-VD
  - Stenosis ≥70%
- Stress Ischemia
  - 5-9.9% of Myocardium
- Stress Ischemia
  - Multiple Segments in 1 Cor. Area
  - No LV Dilation
- STD ≥1mm on ETT with Sx
- CAC Score: 100-399
- 2-VD on CTA:
  - Stenosis 50-69%
NonInvasive Risk Stratification

- Stress Ischemia $\geq 10\%$ of myocardium or $\geq 2$ coronary areas
- Stress Induced LV Dysfunction - $<45\%$ or 10% Drop
- STD $>2$mm at Low Workload or Persisting into Recovery
- Exercise Induced VT, VF, or STE
- LVEF $\leq 35\%$
- CAC Score $>400$ Agaston
- Stress – Induced LV Dilation
- Inducible WMA - 2 Coronary Territories
- Inducible WMA - Low Dose Dobutamine or Low HR $<120$
- LM $\geq 50\%$
- MVD $\geq 70\%$

High Risk: $>3\%$ Annual MI or Death
Class I: Recommendations for Chronic Coronary Disease

- CXR if Atypical Presentation ± Suspected Pulmonary Disease
- Annual Lipids, Glucose, Creatinine
- Carotid Ultrasound - IIa
- Resting ECG after or During Suspected Ischemia
- Ambulatory ECG for Suspected Arrhythmia
- Resting ECG at Presentation
- Echo to Exclude Alternative Causes of Angina, \( \sqrt{ } \) for WMA, and Assess LVEF + Diastolic Function
- Ambulatory ECG Suspected Variant Angina - IIa

Global Strategy of Intervention in Stable Coronary Artery Disease (SCAD) Patients with Demonstrated Ischemia

Significant CAD + Ischemia (>10% myocardium) + OMT

Revascularization possible

Revascularization not possible

Failure

Refractory angina

Anatomical factors
Single multivessel disease; left main; last patent vessel; chronic total occlusion; proximal LAD; syntax score

Clinical factors
Age; gender; diabetes; comorbidities; frailty; LV function; tolerance of meds; clinical scores

Technical factors
Incomplete/complete revascularization; post CABG; post PCI; extensive tortuosity/calcifications

Local factors
Volume/quality of center/operator; patient preference; local cost; availability, waiting lists

CABG
Hybrid
PCI

Stem cell therapy?
Spinal cord stimulation?
External counterpulsation?
Chronic pain syndrome management?
Drug therapy?

Ongoing Follow-Up

Annual Check-Up
- Sx, Function?
- HF, Arrhythmia?
- Risk Factors
- Adequacy of Rx

Class I

Assess LVEF and Segmental WMA in Patients with New or Worsening HF, New MI
Follow-Up Noninvasive Testing in Patients with Known SIHD: New, Recurrent, or Worsening Symptoms not Consistent with Unstable Angina: Recommendations

*Patients able to exercise*

**Class I**

1. Standard exercise ECG testing is recommended in patients with known SIHD who have new or worsening symptoms not consistent with UA and who have a) at least moderate physical functioning and no disabling comorbidity and b) an interpretable ECG. *(Level of Evidence: B)*

Noninvasive Testing in Known SIHD-Asymptomatic (or Stable Symptoms): Recommendations

Class III: No Benefit

1. Nuclear MPI, echocardiography, or CMR, with either exercise or pharmacological stress or CCTA, is not recommended for follow-up assessment in patients with SIHD, if performed more frequently than at a) 5-year intervals after CABG or b) 2-year intervals after PCI. *(Level of Evidence: C)*

### Pretest Likelihood of CAD in Symptomatic Patients According to Age and Sex (Combined Diamond/Forrester and CASS Data)

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Nonanginal Chest Pain</th>
<th>Atypical Angina</th>
<th>Typical Angina</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>30-39</td>
<td>4</td>
<td>2</td>
<td>34</td>
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<tr>
<td>40-49</td>
<td>13</td>
<td>3</td>
<td>51</td>
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<tr>
<td>50-59</td>
<td>20</td>
<td>7</td>
<td>65</td>
</tr>
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<td>60-69</td>
<td>27</td>
<td>14</td>
<td>72</td>
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</table>

Gender Disparity in Coronary Heart Disease: 
Wise - 4-Year Risk-Adjusted Freedom from 
Death or MI by Extent of Disease Category

Event-Free Survival

9.4% death/MI rate with 
only “none” or “minimal” 
disease by angiography

Follow-up Days

0 200 400 600 800 1000 1200 1400 1600

None (<20%) 
(N=317)

Min (20-49%) 
(N=216)

Signif (≥50%) 
(N=330)

2.5%

6.9%

13.6%
Gender Disparity in Coronary Heart Disease: Stable Ischemic Heart Disease

- Women with stable angina (SIHD)
  - ↓ well-being, ↓ ability to perform ADL, ↑ hospitalizations
  - Symptom severity, disability correlate poorly with obstructive CAD
  - Doubled morbidity and mortality vs. men
  - Less severe obstructive coronary disease at angiography

- Complex pathophysiology
  - Obstructive coronary disease
  - Microvascular disease, endothelial dysfunction
  - High atherosclerotic burden – diffuse non-obstructive atherosclerosis with positive remodeling
  - ? Combination
  - ? Other

Vaccarino, NEJM 1999;341:217.
Olson, Eur Heart J 2003;24:1506.
Daly, Circulation 2006;113:490.
Shaw, JACC 2006;47:S4.
Shaw, JACC 2009;54:1561.
SPECT MPI: Basic Principles

• Injection of a radionuclide at rest and stress
• Radionuclide taken up by perfused myocytes
• Gamma particles are released
• Detected by rotating camera (Gamma Camera)
• Rest and Stress images compared
  – Reversible perfusion defect: ischemia
  – Fixed perfusion defect: Infarction
• Useful for:
  – Diagnosis of obstructive CAD
  – Prognosis (Risk Stratification)
SPECT MPI: Protocols

• **Exercise vs. Pharmacologic**
  - Exercise preferable: symptoms, exercise capacity, ST deviation, Duke Treadmill score add additional prognostic information
  - Pharmacologic agents
    - Coronary vasodilators: adenosine, dipyridmole, regadenoson
    - Inotrope/chronotrope: dobutamine

• **ECG Gating – in all cases**
  - Provides LV function/wall motion
    *Fixed perfusion defect + normal wall motion = attenuation
    *Fixed perfusion defect + WMA = infarction

• **Single isotope vs Dual isotope**
  - Single: Tc99m agent at rest and stress
  - Dual: Thallium$^{201}$ at rest, Tc$^{99m}$ at stress
  - Single isotope same day imaging 1/3 radiation dose of Dual isotope imaging
    (~8-12 mSv vs 25-30 mSv)
  - 2 day Tc99m protocols used to give 2 full daily doses to maximize counts/image quality
  - Dual isotope imaging allows delayed imaging for viability assessment

• **Thallium201 Rest- Redistribution Imaging**
  - For viability assessment
SPECT MPI: Radionuclides

✓ Thallium$^{201}$
  - Long $\frac{1}{2}$ Life (73 hours) $\Rightarrow$ lower clinical dose
  - Low energy emitter (68-80 KeV) $\Rightarrow$ more attenuation
  - Lower dose + high attenuation = lower resolution (↓ image quality)
  - Potassium analog - Active transport into/out of myocytes $\Rightarrow$ +Redistribution
  - Allows Viability assessment

✓ Technetium$^{99m}$
  - Examples: Tetrofosmin (Myoview), Sestamibi (Cardiolite)
  - Short $\frac{1}{2}$ life (6 hours) $\Rightarrow$ higher clinical doses
  - High energy emitter (140 KeV) $\Rightarrow$ less attenuation
  - Higher dose + less attenuation = higher resolution (↑ image quality)
  - Passive diffusion into mitochondria $\Rightarrow$ fixed image for $\frac{1}{2}$ life of tracer
  - Optimal SPECT stress imaging tracer
SPECT MPI: Advantages Diagnosis **AND** Prognosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Prognosis</th>
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<tbody>
<tr>
<td>• Presence of disease</td>
<td>• Likelihood of an event</td>
</tr>
<tr>
<td>• Extent and severity of disease</td>
<td>• Type and Severity of an adverse event</td>
</tr>
<tr>
<td></td>
<td>• Incremental prognostic value</td>
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</table>
CASE: Diagnosis

62 yo woman with exertional chest pain

Exercise SPECT MPI:
7 minutes on a Bruce protocol + chest pain
1.5 mm ST depression at peak stress

What do these images suggest?
1) Severe Multi-vessel CAD with high risk features
2) LAD ischemia
3) RCA ischemia, with mild LCX ischemia
4) False positive ECG response
5) Equivocal for CAD due to severe diaphragmatic attenuation
SPECT MPI: Diagnosis of Obstructive CAD

- Test Characteristics compared to angiography
  - Sensitivity
    - Exercise MPI: 82-88%*
    - Pharmacologic MPI: 88-91%*
  - Specificity
    - Exercise MPI: 70-88%*
    - Pharmacologic MPI: 75-90%*
  - Normalcy rate: 90-95%
    - Corrects for decreased specificity due to post-test referral bias.

* Uncorrected for referral bias

ACCF/AHA Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease. JACC 2012
SPECT MPI: Diagnosis of Obstructive CAD
Improved accuracy with Tc$^{99m}$, ECG Gating

Specificity for CAD in women

- Stenosis $> 50%$
  - 201 TL: 71%
  - 99mTc-MIBI: 86%
  - 99mTc-MIBI + Gated: 94%
- Stenosis $> 70%$
  - 201 TL: 67%
  - 99mTc-MIBI: 84%
  - 99mTc-MIBI + Gated: 92%

JACC 1997;29:69-77
CASE: Prognosis

58 yo male with chest pain

No diabetes or prior CAD

Exercise SPECT MPI:
9 minutes on Bruce,
no chest pain, normal ECG

Which of the following characterizes his risk of future CV events?

1) 2% 1-year risk of cardiac death/MI
2) <1% 5 year risk of MI/cardiac death
3) PCI would lower his 1 year risk of MI
4) Balanced ischemia is present, >5% 1 year risk of cardiac death
SPECT MPI: Prognosis
Prognostic value of a NORMAL test

✓ Excellent Negative Predictive Value
0.6% annual event rate for patients with normal studies

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>N</th>
<th>Agent</th>
<th>Average follow-up (y)</th>
<th>Annualized event rate (%)</th>
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<tbody>
<tr>
<td>2003</td>
<td>Elhendy54</td>
<td>218</td>
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<td>Olmos64</td>
<td>225</td>
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<td>2.0</td>
<td>1</td>
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<tr>
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<td>1.3</td>
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<td>1994</td>
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<td>534</td>
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<td>1.1</td>
<td>1.6</td>
</tr>
</tbody>
</table>

SPECT experience: 10 years [median (25th–75th percentile)]

39,173,…
2.3 (1.8–3.0)
0.6 (0.5–0.9)


**Certain populations have worse prognosis for same MPI result
(e.g. prior CAD, diabetes, pharmacologic imaging)
SPECT MPI: Prognosis
Long Term Prognosis of a NORMAL test

Cardiac events: 0.7% per year for 5 years*

*in patients without prior CAD

Normal scan: 5-year Warranty?

Elhhendy et al. J Nuc Card 2003: 10 (3);261-66
SPECT MPI: Prognosis
Defect Severity Predicts Outcome

* P<.001
** P<.01

Event Rate/Year, %

<table>
<thead>
<tr>
<th>SSS</th>
<th>n</th>
<th>Cardiac Death</th>
<th>MI</th>
</tr>
</thead>
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<tr>
<td>&lt;4</td>
<td>2946 Normal</td>
<td>0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>4-8</td>
<td>884 Mildly Abnormal</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>9-13</td>
<td>455 Moderately Abnormal</td>
<td>2.3</td>
<td>2.9</td>
</tr>
<tr>
<td>&gt;13</td>
<td>898 Severely Abnormal</td>
<td>2.9 *</td>
<td>4.2 *</td>
</tr>
</tbody>
</table>

Scan Result

SPECT MPI: Prognosis

Prognostic Impact of Gated SPECT EF

Severely abnormal scan

Cumulative Survival

Follow-up (days)

Mild to moderately abnormal scan

Cumulative Survival

Follow-up (days)

EF ≥ 45%

EF < 45%

P = .000001

P = .006

SPECT MPI: High Risk Features

- Moderate-Severe perfusion defects
  - >10% of myocardium
  - multiple vascular territories
- Markedly abnormal stress ECG response
- Extensive stress-induced wall motion abnormalities
- Reduction from rest to post-stress LVEF ≥5%
- Global LVEF (rest or post-stress) <45%
- Transient ischemic LV dilation (TID)
- Increased TL²⁰¹ lung uptake
- Increased right ventricular uptake at stress

ACCF/AHA Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease. JACC 2012
Pat ID: Patient1
Sex: FEMALE
Limits: AST-FBPdual
TID: 1.20
LHR: 0.35
SSS: 13  SRS: 2  SDS: 11
SS%: 19  SR%: 3  SD%: 16

Proc ID: MPI
View ID: SAX-AST-STR
Date: 2015-08-24 11:38:29
Database: AstonishFemaleStress2
Volume: 28ml (QC=0.00; IR=0.00)
Wall: 82ml
Defect: 19ml
Extent: 24%
TPD: 18%
Shape: 0.59 [SI], 0.81 [Ecc]

Stress Extent (%)
Rest Extent (%)
Reversibility Extent (%)

Str  Rst  Rev
SPECTMPI: Patient Selection Symptomatic Patients

SPECTMPI: Patient Selection
Asymptomatic Patients-Risk Assessment

CHD RISK (Framingham Risk–ATP III)

- Low CHD Risk: Inappropriate
- Intermediate CHD Risk: ECG Interpretable?
  - Yes: Inappropriate
  - No: High CHD Risk:
    - High CHD Risk†: Uncertain
    - No: Appropriate

Positron Emission Tomography (PET)

- Uses radionuclides which decay with positron emission (high energy)
  → High quality images

- Can assess perfusion
  → Superior sensitivity and specificity to SPECT MPI

- Gold standard for viability assessment in nuclear cardiology using $F^{18}$Deoxyglucose (FDG)

- Limitations: Availability, Cost, short tracer $\frac{1}{2}$ life
# Cardiac PET: FDA Approved Radionuclides

<table>
<thead>
<tr>
<th></th>
<th>Rubidium(^{82})</th>
<th>(N^{13})Ammonia</th>
<th>(F^{18}) FDG</th>
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<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Perfusion</td>
<td>Perfusion</td>
<td>Viability</td>
</tr>
<tr>
<td><strong>Production</strong></td>
<td>Generator</td>
<td>Cyclotron</td>
<td>Cyclotron</td>
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<tr>
<td><strong>Physical ½ life</strong></td>
<td>76s</td>
<td>10 min</td>
<td>110 min</td>
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<tr>
<td><strong>Dose</strong></td>
<td>40-60 mCi</td>
<td>10-20 mCi</td>
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<tr>
<td><strong>Radiation</strong></td>
<td>4.1 mSv</td>
<td>3.3 mSv</td>
<td>14 mSv</td>
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<tr>
<td><strong>Mechanism</strong></td>
<td>Potassium analog</td>
<td>Glutamine synthesis</td>
<td>Glucose analog</td>
</tr>
</tbody>
</table>

**Why FDG to assess for viability?**

Cardiac Metabolism: No ischemia \(\text{FFA} > \text{glucose}\)  ➔ Chronic ischemia \(\text{Glucose} > \text{FFA}\)
PET Imaging: CASE

60 yo with LV dysfunction and chronic CAD

Resting PET for perfusion and metabolism (FDG) is performed

These images suggest which of the following is true?

1) Stunned myocardium is present.
2) Hibernating (viable) myocardium is present
3) Transmural myocardial infarction is present.
4) LV function is unlikely to improve with revascularization
Cardiac PET: Viability Imaging

Perfusion Metabolism

Perfusion-Metabolism Mismatch* = Viability
- High likelihood of functional recovery after revascularization

Perfusion Metabolism

Perfusion-Metabolism Match = Non-Viable
- Low likelihood of functional recovery after revascularization

www.asnc/practicepoints