Microvascular Disease: How to Diagnose and What’s its Treatment

Laxmi S. Mehta, MD, FACC
The Ohio State University Medical Center
Assistant Professor of Clinical Internal Medicine
Clinical Director of the Women’s Cardiovascular Health Program
Associate Program Director of Education, Center for Women’s Health

Orlando, Florida – October 7-9, 2011
Gender Differences

The Difference Between Men & Women
Prevalence of Normal Coronary Arteries

- Women have two fold increase in normal coronary arteries regardless of ACS, USA, STEMI

<table>
<thead>
<tr>
<th>Condition</th>
<th>Women</th>
<th>Men</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute coronary syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GUSTO²</td>
<td>343/1768 (19.4)</td>
<td>394/4638 (8.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TIMI 18³</td>
<td>95/555 (17)</td>
<td>99/1091 (9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Unstable angina²</td>
<td>252/826 (30.5)</td>
<td>220/1580 (13.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TIMI III³</td>
<td>30/113 (26.5)</td>
<td>27/278 (8.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MI without ST-segment elevation²</td>
<td>41/450 (9.1)</td>
<td>55/1299 (4.2)</td>
<td>.001</td>
</tr>
<tr>
<td>MI with ST-segment elevation²</td>
<td>50/492 (10.2)</td>
<td>119/1759 (6.8)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; MI, myocardial infarction; TIMI, Thrombosis In Myocardial Infarction.
Women’s Ischemia Syndrome Evaluation (WISE) Study

- A four-center NHLBI-sponsored study
- 936 women undergoing clinically ordered coronary angiography
- Chest pain, myocardial ischemia documented on noninvasive testing
62% of Women Undergoing Diagnostic Angiography Have No or Minimal Stenosis

- "Severe" or ≥50% stenosis: 38%
- "None" or <20% stenosis: 37%
- "Minimal" or 20%-49% stenosis: 25%

Microvascular Disease
Exertional angina

Abnormal SPECT

No obstructive CAD
Abnormal CFR and increased LVEDP

Diffuse Atherosclerosis by IVUS
WISE: Persistent chest pain in women predicts future CV events

n = 673 WISE participants with chest pain at baseline

Event-free survival (%)

Years from PChP diagnosis (at one year)

With CAD
HR 1.17 (0.76–1.80)
P = 0.49

Without CAD
HR 1.89 (1.06–3.39)
P = 0.03

PChP = persistent chest pain

Subgroup of Cardiac Syndrome X

- Cardiac syndrome X: persistent chest pain, evidence of angina, and ischemic-type ST-segment depression or noninvasive perfusion or wall-motion abnormality during stress testing.
  - early reports suggested a benign prognosis

- WISE: up to 50% of these patients may have MCD, which is associated with an adverse prognosis

- Patients with MCD frequently have atherosclerosis on intravascular coronary ultrasound and face a 2.5% annual adverse cardiac event rate which includes MI, CVA, hosp for CHF, SCD.

- Thus, MCD appears to be a high-risk subgroup within CSX.
Resistance to myocardial blood flow in downstream vessels

Microvascular dysfunction may include the following:

1. Altered resting vascular smooth muscle tone secondary to either endothelial or smooth muscle cell dysfunction
2. Altered responses to constrictor or dilator stimuli
3. Reduced number of arterioles and capillaries (eg, rarefaction)
4. Structural alterations that contribute to decreased lumen size, increased wall-to-lumen ratio, increased stiffness, and remodeling
Intracoronary Doppler blood flow velocity waveforms in response to intracoronary adenosine and acetylcholine.

Coronary Flow Reserve (CFR) =

\[
\frac{\text{Peak Average Peak Velocity (PAPV)}}{\text{Baseline Average Peak Velocity (BAPV)}}
\]

Coronary Blood Flow Reserve (CBF) =

\[
\frac{\text{Peak } 3.1487 \times \text{ (coronary artery diameter in mm}/2) \times 2 \times (\text{average peak velocity}/2)}{\text{Baseline } 3.1487 \times \text{ (coronary artery diameter in mm}/2) \times 2 \times (\text{average peak velocity}/2)}
\]

Bairey Merz C N, Pepine C J Circulation 2011;124:1477-1480
Intracoronary acetylcholine (ACH) demonstrating constriction of the coronary arteries (arrow) and intracoronary nitroglycerin (NTG) coronary angiography demonstrating dilation.

Normal: dilates   Abnormal: Vasoconstriction

Baseline  Post ACH  Post NTG
P-31 Spectroscopy: Metabolic Dysfunction

- Phosphorus-31 nuclear magnetic resonance spectroscopy (MRS);
- Normal PCr/ATP ratio \(\approx 1.6\)
- 74 WISE women w/o CAD.
- PCr/ATP ratio measured before & after handgrip stress
- Abnormal defined \(< 20\% \text{ change}\)
- Measure of metabolic function in heart muscle

Spectra from Woman Volunteer:
A) LV chamber
B) Interventricular septum
C) LV anterior wall
P-31 Spectroscopy & Outcomes

Source: Johnson, Circulation 2004

Risk adjusted p=0.02
Perfusion CMR in Cardiac Syndrome-X

Digitized Retinal Photographs Showing Examples of Low vs High Arteriole-to-Venule Ratio (AVR)

Goals of therapy

1. Antiatherosclerosis and antianginal medications to reduce cardiac events
2. Relief of angina to improve outcomes.
Strategies for atherosclerosis and endothelial dysfunction
- ACE-I/ARBs
- Statins
- Low-dose aspirin

Antianginal therapy
- β-Blockers
- CCBs
- Nitrates
- Ranolazine
- ECP

Additional symptom management
- Tricyclic medication
- Hypnosis
- Spinal cord stimulation

MCD
- Persistent angina
- Evidence of ischemia
- No obstructive CAD

Persistent symptoms?

Therapeutic lifestyle change
- Smoking cessation
- Nutrition
- Physical activity
- Weight management

- Improved quality of life?
- Decreased morbidity and mortality?
- Decreased health care costs?
Ranolazine: Study Design Flow Diagram

- Qualifying CMR
- Baseline SAQ & DASI
  - Enrollment & Randomization
  - Treatment Period 1 (Up to 24 Months)
- CMR, SAQ, & DASI
  - Washout
  - Treatment Period 2 (4 Weeks)

Ranolazine and CFR

![Graph showing MPRI Change vs CFR with p = 0.040 for CFR (n = 13) categories]

- MPRI Change
  - 2.5
  - 2.6-3.0
  - >3.0

- p = 0.040
Effect of Ranolazine
<table>
<thead>
<tr>
<th></th>
<th>Ranolazine</th>
<th>Placebo</th>
<th>Treatment Effect (p Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>91.7 (79.2, 97.9)</td>
<td>83.3 (66.6, 97.2)</td>
<td>0.046</td>
</tr>
<tr>
<td>Angina stability</td>
<td>75.0 (50.0, 100.0)</td>
<td>50.0 (25.0, 75.0)</td>
<td>0.008</td>
</tr>
<tr>
<td>Angina frequency</td>
<td>80.0 (50.0, 100.0)</td>
<td>75.0 (60.0, 87.5)</td>
<td>0.197</td>
</tr>
<tr>
<td>Treatment satisfaction</td>
<td>87.5 (75.0, 100.0)</td>
<td>93.8 (75.0, 100.0)</td>
<td>0.058</td>
</tr>
<tr>
<td>Quality of life</td>
<td>75.0 (60.4, 83.3)</td>
<td>66.7 (58.3, 75.0)</td>
<td>0.021</td>
</tr>
</tbody>
</table>
Conclusions

- Traditional diagnostic tests for obstructive coronary disease are not as reliable in women, higher incidence of “false positive” tests.
- In women, atherosclerosis may not be focal epicardial lesion. Nonobstructive disease cannot be ignored.
- Assessment of microvascular disease can be complex.
- Persistent chest pain is a poor prognostic factor.
- Treatment similar to epicardial disease