Non-Obstructive Coronary Artery Disease in Women

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Disclosures

- None

Magnitude of the Problem

- Cardiovascular disease is a leading cause of morbidity and mortality in women, regardless of race or ethnicity.
- The leading cause of death - ischemic heart disease and stroke.
- 2 out of 3 women who have a heart attack never fully recover.
- Among women who survive an attack, 46% are disabled with heart failure within 6 years.

Mosca L et al. Circulation 2011;123
Ischemic Heart Disease in Women

- Younger women --
  - Higher mortality after MI than men
  - Lower decline in IHD mortality
  - MI incidence increasing
  - Unexplained by traditional risk factors
  - Less obstructive CAD on angiography --- MINOCA (10-15% of ACS, 1-year prognosis is ~5% for all cause)

- Each year in US:
  - >10,000 MIs in women <45 years
  - >100,000 MIs in women <65 years

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Women are NOT little Men

<table>
<thead>
<tr>
<th>Women are NOT little Men</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous Coronary Artery Dissection</td>
<td>More</td>
<td></td>
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<tr>
<td>Diabetic Heart Failure</td>
<td>More</td>
<td></td>
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<tr>
<td>Pulseless Electrical Activity</td>
<td>More</td>
<td></td>
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<tr>
<td>Stress/Takotsubo Cardiomyopathy</td>
<td>More</td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction: Embolic &gt; Plaque Rupture</td>
<td>More</td>
<td></td>
</tr>
</tbody>
</table>
| Risk Factor Differences:
  - Triglycerides
  - Diabetes | Stronger | Stronger |
| Postural orthostatic tachycardia syndrome (POTS) | More | |
| Ischemia and No Obstructive CAD – endothelial dysfunction/coronary microvascular dysfunction | More | |

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<table>
<thead>
<tr>
<th>Women are NOT little Men</th>
<th>Women</th>
<th>Men</th>
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</thead>
<tbody>
<tr>
<td>Autoimmune-related CVD</td>
<td>More</td>
<td></td>
</tr>
<tr>
<td>Psychosocial risk factors &amp; CVD: Depression, domestic violence, stress, abuse</td>
<td>More</td>
<td></td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>More</td>
<td></td>
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<tr>
<td>Sudden cardiac death with structurally normal heart</td>
<td>More</td>
<td></td>
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<tr>
<td>Pregnancy-related disorders</td>
<td>More</td>
<td></td>
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<tr>
<td>Post-procedural complications</td>
<td>More</td>
<td></td>
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<tr>
<td>Abnormal Cardiac Nociception</td>
<td>More</td>
<td></td>
</tr>
<tr>
<td>Treatments: Cardiac Rehabilitation, ICD therapy, OMT</td>
<td>Less</td>
<td></td>
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<tr>
<td>Functional Disability from IHD</td>
<td>More</td>
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</table>
## IHD Risk Factors in Women

<table>
<thead>
<tr>
<th>Traditional Risk Factors</th>
<th>Emerging Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Age</td>
<td>✓ Ethnicity</td>
</tr>
<tr>
<td>✓ Hypertension</td>
<td>Adverse Pregnancy</td>
</tr>
<tr>
<td>✓ Dyslipidemia</td>
<td>Outcomes</td>
</tr>
<tr>
<td>✓ Diabetes</td>
<td>Autoimmune diseases</td>
</tr>
<tr>
<td>✓ Obesity</td>
<td>Premature Menopause</td>
</tr>
<tr>
<td>✓ Smoking</td>
<td>Radiation/Chemotherapy</td>
</tr>
<tr>
<td>Family History</td>
<td>Obstructive Sleep Apnea</td>
</tr>
<tr>
<td>Physical Inactivity</td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Psychosocial factors</td>
</tr>
<tr>
<td></td>
<td>Environmental</td>
</tr>
</tbody>
</table>

## Chest Pain without Obstructive CAD

Marinescu MA et al., JACC Cardiovascular Imaging 2015.

## Ischemia and No Obstructive Coronary Arteries (INOCA): Major Clinical Problem

- Patient presents with Angina (typical or atypical)
  - Chest pain/pressure, dyspnea, dizziness, left arm or jaw pain, nausea, weakness, unusual fatigue, etc
- Evidence of myocardial ischemia
  - EKG changes and/or troponin positive
  - Abnormal cardiac stress testing
- Cardiac catheterization - (anatomy)
  - Open arteries
  - No obstructive coronary artery disease (<50% stenosis)
Ischemia and No Obstructive CAD (INOCA)

- ~2/3 of women suspected of ischemia have no obstructive CAD on angiography.
- INOCA is not benign - death, MI, stroke, and HF hospitalizations.
- ~50% with INOCA have coronary microvascular dysfunction (CMD). ~3 million U.S. women
- No clear clinical practice management guidelines
- High healthcare utilization/costs – repeat cardiac stress testing and repeat angiograms
- Disability, poor satisfaction and quality of life
- Psychosocial risk factors – depression, anxiety

Prevalence of No Obstructive CAD in Acute Coronary Syndrome Studies

![Graph showing prevalence of No Obstructive CAD in acute coronary syndrome studies.]


Prognosis of No Obstructive CAD

- N = 540 (WISE)
- Compared to 1000 age and race-matched controls (WTH)

![Graph showing annualized event rate.]

WISE Study: Typical Angina and Functional Disability in Women

5-Year Rates of Functional Disability

- Typical angina (pre-e)
- Functional disability (>4 MET)

Bairey Merz et al. Circ 2017

Diagnostic Criteria of MINOCA

1. Acute MI criteria, including:
   a. Positive cardiac biomarker: defined as a rise and/or fall in serial levels, with at least 1 value above the 99th percentile upper reference limit.
   b. Clinical evidence of MI, including any of the following:
      i. Ischemic symptoms (chest pain and/or dyspnea)
      ii. Ischemic ECG changes (new ST segment changes or left bundle branch block)
      iii. New pathological Q-waves
      iv. New loss of viable myocardium on myocardial perfusion imaging or
      v. New regional wall motion abnormality on left ventricular imaging

2. Non-obstructive coronary artery disease on angiography
   Defined as the absence of obstructive coronary artery disease on angiography. (ie. no coronary artery stenosis >50%, in any potential infarct-related artery). This includes both patients with
   - normal coronary arteries (no stenosis >50%)
   - mild coronary atherosclerosis (stenosis >50% but <50%)

3. No clinically overt-specific cause for the acute presentation
   Defined as the time of angiography, the underlying cause of the clinical presentation and myocardial injury is not apparent

Beltrame JH Sept 2017
What is the Prevalence of MINOCA?
10-15% of Acute MI presentations

Which Population Predominates in MINOCA?
Women
Younger age

Prognosis of MINOCA
- Current estimates for 1 year after MINOCA
  - 5% of all cause mortality
  - 25% with recurrent angina

Pathophysiologic Mechanisms- MINOCA
- Underlying pathophysiological mechanisms of MINOCA
- Coronary causes
  1. Vasospastic angina (prinzmetal's variant)
  2. Coronary Microvascular Disorders
     a. Coronary microvascular dysfunction
     b. Microvascular angina
  3. Coronary plaque disruption
  4. Sudden coronary thrombosis/embolism
  5. Mixed obstructive CAD
- Non-Coronary causes
  1. Myocardial Disorders
  2. Takotsubo cardiomyopathy
  3. Other cardiomyopathies (DCM, RCM)
  4. Non-Coronary Disorders
     a. Pulmonary embolism
     b. Renal impairment
     c. Stroke
     d. Septic
Cardiac Magnetic Resonance Imaging in MINOCA

1. Patients who self-refer or are referred by treating cardiologist after unexplained NSTEMI (no obstructive CAD on angiogram)
2. Recurrent rest, emotional stress-induced, or exertional angina
3. Several weeks post-PTCA and have “open” arteries who continue to have angina
4. Younger/peri-menopausal age range (45-55) who have signs and symptoms of ischemia
5. Women with risk factors such as h/o pre-eclampsia, chemotherapy, chest wall radiation, autoimmune disorders (i.e. lupus), migraines or Raynaud’s

Typical Scenarios

1. Patients who self-refer or are referred by treating cardiologist after unexplained NSTEMI (no obstructive CAD on angiogram)
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Coronary Microvascular Dysfunction (CMD)

* Term used to describe abnormalities in regulation of myocardial blood flow not explained by epicardial atherosclerosis.

• CMD can be from endothelial dependent or independent mechanisms.

Coronary Vascular Resistance

- Epicardial arteries normally contribute <10% of the coronary vascular resistance
- Coronary microvasculature is responsible for >70% of the coronary resistance under physiological circumstances.


Functional Coronary Anatomy

- Epicardial and proximal arteries - little resistance to flow; maintain a level of shear stress by endothelial-dependent vasodilation.
- Pre-arterioles = extramyocardial, and thicker wall than arterioles – myogenic vasoconstriction to maintain flow (sympathetic control)
- Arterioles - high resting tone, dilate to metabolites


De Bruyne B et al. JACC 2016;67(10)
Coronary endothelial dysfunction is a pathological condition

Risk factors and Oxidative stress - Imbalance of factors

- Vasodilation
- Anti-proliferation
- Anti-thrombosis
- Anti-inflammatory
- Anti-oxidant
- Vasoconstriction
- Proliferative
- Pro-thrombotic
- Pro-coagulant
- Pro-inflammatory

Mechanisms of Myocardial Ischemia

Structural Features (macro- and micro- vessels)
- Smaller size
- Increased stiffness (fibrosis, remodeling, etc)
- More diffuse disease
- More plaque erosion versus rupture
- Microemboli
- Capillary rarefaction (dropout)

Functional Features (macro- and micro- vessels)
- Endothelial dysfunction
- Smooth muscle dysfunction (Raynaud’s, migraine, coronary artery spasm)
- Inflammation
- Vasculitis (Takayasu’s arteritis, neutrophilic, SLE, giant cell, etc)

Gender Differences in Ischemic Heart Disease in Women

Pursue non-invasive stress testing for objective evidence of ischemia

- Is patient able to exercise?
- Is baseline EKG ok to pursue ETT (no LVH, LBBB, etc)?
- If yes, start with ETT:
  - Elicit symptoms
  - Detection of Ischemic EKG changes
  - METS and functional capacity
  - Arrhythmias
  - Hypertensive response to exercise

If ETT inconclusive and/or persistent symptoms

- Add an imaging test
  - Stress Echo (diastolic function, hypertrophy, pulmonary hypertension, valvular problems, WMA)
  - Stress PET-CT with Coronary Flow Reserve (added benefit of CAC)
  - Adenosine Stress Cardiac Magnetic Resonance Imaging (added benefit of scar imaging and best for tissue characterization)

Negative Non-invasive Test Does Not Rule Out Coronary Vasoconstriction

<table>
<thead>
<tr>
<th>Test</th>
<th>N</th>
<th>% (CI)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>NPV (95% CI)</th>
<th>PPV (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Exercise Echocardiogram</td>
<td>99</td>
<td>40.4</td>
<td>33 (26-51)</td>
<td>36 (24-48)</td>
<td>36 (16-73)</td>
<td>36 (16-73)</td>
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<tr>
<td>Dobutamine Echocardiogram</td>
<td>23</td>
<td>33.3</td>
<td>26 (9-59)</td>
<td>37 (16-66)</td>
<td>26 (5-95)</td>
<td>38 (14-84)</td>
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<tr>
<td>Exercise PETCT</td>
<td>111</td>
<td>38.2</td>
<td>40 (25-51)</td>
<td>30 (19-79)</td>
<td>30 (19-79)</td>
<td>30 (19-79)</td>
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<tr>
<td>VAS lase PETCT</td>
<td>44</td>
<td>30.8</td>
<td>30 (15-46)</td>
<td>42 (24-59)</td>
<td>30 (15-46)</td>
<td>42 (24-59)</td>
</tr>
<tr>
<td>VAS lase PET</td>
<td>33</td>
<td>36.4</td>
<td>35 (16-57)</td>
<td>35 (16-57)</td>
<td>28 (11-52)</td>
<td>42 (25-80)</td>
</tr>
<tr>
<td>A1 imaging</td>
<td>361</td>
<td>41.4</td>
<td>41 (16-75)</td>
<td>31 (9-60)</td>
<td>31 (9-60)</td>
<td>31 (9-60)</td>
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<tr>
<td>Exercise TEE</td>
<td>292</td>
<td>30.1</td>
<td>30 (15-46)</td>
<td>40 (16-75)</td>
<td>40 (16-75)</td>
<td>30 (15-46)</td>
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<tr>
<td>A1 imaging + EEG</td>
<td>361</td>
<td>63.2</td>
<td>63 (47-79)</td>
<td>35 (23-49)</td>
<td>35 (23-49)</td>
<td>63 (47-79)</td>
</tr>
</tbody>
</table>

• No vasoconstrictive stimulus for clinical non-invasive testing (such as mental stress, cold pressor, hyperventilation, etc)

Coronary Reactivity Testing:
Adenosine

APV = Average Peak Velocity
CBF = Cross section area of coronary artery X APV/2

Macrovascular Coronary Function

Baseline  Acetylcholine  Nitroglycerin

CRT Safety Data: Out of 293 women, no CRT-related mortality. 0.7% serious adverse events: 1 had dissection, and 1 developed MI from coronary spasm. MACE rate at 5.4 year follow up 8.2%


WISE Study Coronary Reactivity Testing Protocol

ADO 18 mcg  18 mcg  36 mcg
ACH 0.364 mcg  36.4 mcg  108 mcg
NTG 200 mcg

**Not done in the setting of ACS
**Higher ACH doses are used in other countries

### Components of Coronary Reactivity Testing

<table>
<thead>
<tr>
<th></th>
<th>Microvascular Dysfunction</th>
<th>Macrovascular Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Endothelial</td>
<td>CFR &lt; 2.5</td>
<td>Coronary dilation &lt; 20%</td>
</tr>
<tr>
<td>Dependent</td>
<td>to Adenosine</td>
<td>to Nitroglycerin</td>
</tr>
<tr>
<td>Endothelial</td>
<td>∆CBF &lt; 50%</td>
<td>Coronary dilation ≤ 0%</td>
</tr>
<tr>
<td>Dependent</td>
<td>to Acetylcholine</td>
<td>to Acetylcholine</td>
</tr>
<tr>
<td>Coronary Spasm</td>
<td>Chest pain + ECG changes + significant constriction to Acetylcholine</td>
<td></td>
</tr>
</tbody>
</table>

Barry Marz CN et al., Circulation. 2017;135(11):1075-1092

### Coronary Flow Reserve to Adenosine Predicts Adverse Outcomes

**Women without CAD**

![Graph showing event-free survival over years follow-up for CFR ≥ 2.0 vs. CFR < 2.0.](source: Pepine CJ et al., JACC 2010)

### Endothelial Dysfunction Predicts Cardiovascular Events

![Graph showing correlation between endothelial dysfunction and cardiovascular events.](source: Von Mering GO et al., Circulation. 2004;109:722-725; Lerman A, et al., Circulation. 2005;111:363-368)
Provocative spasm testing in patients with MINOCA


Vascular Manifestations – Inflammatory Disorders


Mechanisms of CMD that Trigger Events in Inflammatory Conditions

Myocardial Blood Flow and Chronic Inflammation


Tavella R et al. IJC 2018;267:54-55

<table>
<thead>
<tr>
<th>Pathophysiologic mechanism</th>
<th>Clinical investigation</th>
<th>Potential therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary plaque disruption</td>
<td>• Optical coherence tomography</td>
<td>• Statins</td>
</tr>
<tr>
<td></td>
<td>• Plaque erosion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Plaque rupture</td>
<td></td>
</tr>
<tr>
<td>Coronary thromboembolism</td>
<td>• Optical coherence tomography</td>
<td>• Anti-platelet agents</td>
</tr>
<tr>
<td></td>
<td>• Thrombosis</td>
<td>• Anticoagulants</td>
</tr>
<tr>
<td></td>
<td>• Embolism</td>
<td></td>
</tr>
<tr>
<td>Coronary vasomotor dysfunction</td>
<td>• Provocative spasm testing</td>
<td>• Calcium channel blockers</td>
</tr>
<tr>
<td></td>
<td>• Coronary artery spasm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Microvascular dysfunction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Coronary flow reserve</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Microvascular resistance indices</td>
<td></td>
</tr>
</tbody>
</table>

Tavella R et al. IJC 2018;267:54-55

Treatment

- Tobacco cessation
- Cardiac Rehabilitation – Angina/IHD
- Mediterranean diet
- Sleep hygiene/treat sleep apnea
- Treat risk factors – DM, HTN, Hyperlipidemia, etc
- Stress management/depression treatment
Brain-Heart Connection

- Mental stress myocardial ischemia
- Takotsubo Cardiomyopathy

IHD Risk Factors in Women

- Hormonal factors: Polycystic Ovaries, Hypoestrogenemia, Menopause, Hormone Therapy
- Psychosocial factors
- Genetic predisposition, family history
- Endothelial Dysfunction, Autonomic Dysfunction, Immune Dysfunction, Inflammation, Thrombosis

Therapy in CMD

- Coronary Endothelial Dysfunction
  - ACE-I, statins, L-arginine, aerobic exercise, ECGP

- Abnormal CFR
  - beta-blockers/alpha-beta blockers, ACE-I

- Abnormal Smooth Muscle/Vasospasm
  - calcium channel blockers, nitrates, rho kinase inhibition

- Anti-Anginal/Anti-Ischemic
  - ranolazine, ivabradine, xanthine derivatives, nicorandil

- Abnormal Cardiac Nociception
  - Low dose tricyclic, spinal cord stimulation, stellate ganglion block, cognitive behavioral therapy
Psychosocial Factors

- Low Socioeconomic Status/Income
- Mental Stress
- Work/Job Stress
- Anxiety
- Depression/hopelessness
- Anger
- Hostility
- Smaller social networks/social isolation
- Caregiver strain
- Early life adversity
- Optimism (protective)

Young Women with Recent MI Have More Psychosocial/Behavioral Risk Factors Than Men

Myocardial Infarction and Mental Stress Study 1 (MIMS1)

No Difference in Traditional CHD Risk Factors

Myocardial Infarction and Mental Stress Study 1 (MIMS1)
Mental Stress Induced Myocardial Ischemia (MSIMI)

- Powerful emotions trigger Angina/MIs
- 3X MACE (independent of cardiac risk factors or presence of exercise-induced ischemia)
- Different mechanism compared to exercise stress—doesn’t always accompany physical (exercise/pharm) stress ischemia
- Independent of CAD severity
- Correlates with daily life ischemia
- Marker of susceptibility to emotional stress

Young Women with MI Have More Mental Stress-Induced Myocardial Ischemia

- 98 men and women ≤ 60 years
- MI in previous 6 months
- SPECT with [99mTc] sestamibi at rest, mental stress, exercise/pharmacologic stress
- No sex differences in exercise-stress ischemia
Cardiac Autonomic Nervous System (CANS) Study: Mental Stress Testing Protocol

- Women with Coronary Vascular Dysfunction (Functional Angiogram)
- Asymptomatic Controls: Age and BMI matched, no risk factors, and normal ETT

Hemodynamic Changes to Mental Stress

<table>
<thead>
<tr>
<th></th>
<th>Cases Median [min, max] n = 44</th>
<th>Reference Control Median [min, max] n = 17</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>HR 97 [47, 96]</td>
<td>91 [50, 97]</td>
<td>0.22</td>
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<tr>
<td></td>
<td>SBP 115 [90, 145]</td>
<td>116 [94, 145]</td>
<td>0.50</td>
</tr>
<tr>
<td>Anger</td>
<td>HR 12 [2, 42]</td>
<td>11 [8, 53]</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>SBP 10 [2, 59]</td>
<td>18 [4, 59]</td>
<td>0.89</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>HR 18 [-6, 41]</td>
<td>17 [-6, 41]</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>SBP 17 [-4, 62]</td>
<td>23 [-6, 39]</td>
<td>0.23</td>
</tr>
<tr>
<td>Cold Presser</td>
<td>HR 1 [2, 30]</td>
<td>-1 [-14, 17]</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>SBP 16 [-6, 64]</td>
<td>21 [-4, 40]</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Greater Mental Stress Peripheral Vasoreactivity in Women with Coronary Vascular Dysfunction

Peripheral vasoconstriction inversely correlated with anxiety (r=-3.4, p=0.03), frustration (r=-0.37, p=0.02), & feeling challenged (r=-0.37, p=0.02) in cases but not controls.
Conclusions

- Ischemia and no obstructive coronary artery disease (INOCA) is highly prevalent and not benign.
- A subgroup of INOCA patients have coronary microvascular dysfunction (CMD), which is associated with adverse CV outcomes.
- Anti-anginal, anti-atherosclerotic, and anti-ischemic therapies, as well as non-pharmacologic approaches can be helpful.
- Large, randomized, therapeutic clinical trials in CMD are lacking, partly due to its heterogeneous nature, and partly because of lack of diagnostic criteria.

Thank You!

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