Women and Heart Disease

The Very Latest in Cardiovascular Medicine and Surgery

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“What man can pretend to know the riddle of a woman’s mind?”

-Miguel de Cervantes Saavedra, Don Quixote
Disclosures

- None
Key Concepts

- Compare biologic basis for differences in cardiovascular diseases in women and men
- Discuss the critical need for research to define best practices for diagnosis and treatment
Mortality Trends
Cardiovascular Disease Mortality Trends
for Women and Men
United States, 1979-2011
Risk of Developing Heart Disease in the Next 10 Years
Among Women Ages 30-74

Source: Yang et al., American Journal of Preventive Medicine, 2014
Ischemic Heart Disease
Differences in Women and Men

• Develop manifestations 10 years after men
• Higher prevalence of angina
• Lower burden of obstructive CAD on angiography
  – 2/3 women failed to exhibit obstructive CAD during clinically ordered angiograms for signs and symptoms of ischemia (WISE)
• Worse prognosis
Women are more likely than men to have MI symptoms unrelated to chest pain, such as:

- Neck, jaw, shoulder, upper back or abdominal pain
- Shortness of breath
- Nausea and vomiting
- Sweating
- Lightheadedness or dizziness
- Unusual fatigue
AHA Scientific Statement

Acute Myocardial Infarction in Women
A Scientific Statement From the American Heart Association

Laxmi S. Mehta, MD, FAHA, Chair; Theresa M. Beckie, PhD, FAHA, Co-Chair; Holli A. DeVon, PhD, RN, FAHA; Cindy L. Grines, MD; Harlan M. Krumholz, MD, SM, FAHA; Michelle N. Johnson, MD, MPH; Kathryn J. Lindley, MD; Viola Vaccarino, MD, PhD, FAHA; Tracy Y. Wang, MD, MHS, MSc, FAHA; Karol E. Watson, MD, PhD; Nanette K. Wenger, MD, FAHA; on behalf of the American Heart Association Cardiovascular Disease in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Cardiovascular and Stroke Nursing, and Council on Quality of Care and Outcomes Research
Mechanisms of MI in Women Without Obstructive CAD

Patient flow and proportion with plaque disruption


50 Patients

42 IVUS

CMR not done*

36 IVUS and CMR

6 IVUS Only

8 CMR Only

8 Patients gave consent after angiography without IVUS**

16 had plaque rupture (11), ulceration (4), or both (1), 38% plaque disruption

- All patients initially consented to CMR but then declined
- ** includes 5 patients with STEMI
### Plaque Erosion vs. Plaque Rupture

<table>
<thead>
<tr>
<th>Plaque erosion</th>
<th>Plaque rupture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid poor</td>
<td>Lipid rich</td>
</tr>
<tr>
<td>Proteoglycan and glycosaminoglycan rich</td>
<td>Collagen poor, thin fibrous cap</td>
</tr>
<tr>
<td>Non-fibrillar collagen breakdown</td>
<td>Interstitial collagen breakdown</td>
</tr>
<tr>
<td>Few inflammatory cells</td>
<td>Abundant inflammation</td>
</tr>
<tr>
<td>Endothelial cell apoptosis</td>
<td>Smooth muscle cell apoptosis</td>
</tr>
<tr>
<td>Secondary neutrophil involvement</td>
<td>Macrophage predominance</td>
</tr>
<tr>
<td><strong>Female</strong> predominance</td>
<td><strong>Male</strong> predominance</td>
</tr>
<tr>
<td>High triglycerides</td>
<td>High LDL</td>
</tr>
</tbody>
</table>

**Thrombus**
- Lipid
- Lumen
- Fibrous cap
- Matrix
- Media
Plaque Rupture and Plaque Erosion
Cardiac Optical Coherence Tomography

A

B

C

D

P

L

T
CMR images
LGE with corresponding end diastolic cine image
Spontaneous Coronary Artery Dissection

- 80% of these patients are women
- Associated with peripartum, systemic vasculopathies, FMD
- Treatment?
- 10 year recurrence up to 29%
Coronary Vasospasm

- Likely multifactorial pathogenesis
- Smoking cessation
- Vasodilator therapy
Takotsubo Cardiomyopathy

Apical Ballooning Syndrome

1. Transient akinesis or dyskinesis of the LV apical and midventricular segments, extending beyond a single epicardial vascular distribution

2. Absence of obstructive CAD or angiographic evidence of acute plaque rupture

3. New EKG abnormalities

4. Absence of:
   - Recent severe head trauma
   - Intracranial bleeding
   - Pheochromocytoma
   - Myocarditis
   - Hypertrophic cardiomyopathy
### Table 2. Plasma Catecholamine and Neuropeptide Levels.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with Stress Cardiomyopathy (N=13)</th>
<th>Patients with Killip Class III Myocardial Infarction (N=7)</th>
<th>Normal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1 or 2</td>
<td>Day 3, 4, or 5</td>
<td>Day 7, 8, or 9</td>
</tr>
<tr>
<td>Catecholamine precursor (pg/ml)</td>
<td>2859 (2721–2997)†</td>
<td>2405 (2386–2761)†</td>
<td>1656 (1065–2101)</td>
</tr>
<tr>
<td>Epinephrine (pg/ml)</td>
<td>1264 (916–1374)†</td>
<td>1944 (733–1118)†</td>
<td>348 (180–150)</td>
</tr>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>2214 (5709–2510)†</td>
<td>1373 (1231–2389)†</td>
<td>1142 (1235–1252)</td>
</tr>
<tr>
<td>Dopamine (pg/ml)</td>
<td>111 (106–146)‡</td>
<td>77 (63–110)</td>
<td>56 (47–77)</td>
</tr>
<tr>
<td>Neuronal metabolites (pg/ml)</td>
<td>2706 (2382–3313)‡</td>
<td>2689 (2246–2842)‡</td>
<td>2161 (2093–2416)$</td>
</tr>
<tr>
<td>Dihydroxyphenylglycol</td>
<td>2753 (2573–3077)‡</td>
<td>2598 (2354–2892)‡</td>
<td>1345 (1194–1682)</td>
</tr>
<tr>
<td>Peptides (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropeptide-Y (pg/ml)</td>
<td>186 (162–236)$</td>
<td>185 (158–214)†</td>
<td>136 (90–182)$</td>
</tr>
<tr>
<td>Brain natriuretic peptide</td>
<td>1033 (905–1783)$</td>
<td>450 (205–684)</td>
<td>142 (72–236)</td>
</tr>
<tr>
<td>Serotonin and metabolite (pg/ml)</td>
<td>2585 (2165–2816)‡</td>
<td>2379 (2290–2900)‡</td>
<td>1602 (864–1989)</td>
</tr>
<tr>
<td>5-Hydroxytryptamine</td>
<td>7839 (5698–9644)</td>
<td>7849 (5089–9644)</td>
<td>6471 (3308–7074)</td>
</tr>
</tbody>
</table>

* All P-values are for comparison of levels in patients with Killip class III myocardial infarction measured at similar times.  
† P<0.005  
‡ P<0.01  
§ Data are from Goldstein et al.  
¶ Data are from Onouha et al.  
|| Data are from Redfield et al.  
** Data are from Spreux-Varoquaux et al.
Microvascular Dysfunction

What happens to freeway flow if the freeway is open but the off-ramps are closed?

 Syndrome X

- Stable ischemic syndrome resulting from endothelial and/or microvascular dysfunction without obstructive CAD
Physiologic Lesion Assessment

Two-Compartment Model of Coronary Circulation

Invasive and quantitative method for evaluating the micro-circulation:

- **FFR**: Specific for epicardial disease
- **CFR**: Affected by both epicardial and microcirculatory disease

![Diagram showing how to interpret CFR and FFR results](image)
WISE
(Women’s Ischemia Syndrome Evaluation)
Prospective cohort study conducted at 4 US sites

• Improve diagnostic testing for ischemic heart disease in women

• Study pathophysiologic mechanisms for ischemia in the absence of epicardial coronary artery stenosis

• Evaluate the influence of menopausal status and reproductive hormone levels on diagnostic testing

Decisive Findings From the WISE

• >50% of women referred for evaluation of ischemia do not have obstructive coronary disease

  – Prognosis for these women is intermediate for future adverse cardiac events and persistent symptoms

• Physicians should no longer ignore nonobstructive coronary angiograms in women

• Physicians should not call an abnormal perfusion test with nonobstructive coronary artery disease a false positive

Effect of Potentially Modifiable Risk Factors associated with MI in 52 Countries:
The INTERHEART Study
<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Sex</th>
<th>Control (%)</th>
<th>Case (%)</th>
<th>Odds ratio (99% CI)</th>
<th>PAR (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoking</td>
<td>F</td>
<td>9.3</td>
<td>20.1</td>
<td>2.86 (2.36–3.48)</td>
<td>15.8% (12.9–19.3)</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>33.0</td>
<td>53.1</td>
<td>3.05 (2.78–3.33)</td>
<td>44.0% (40.9–47.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>F</td>
<td>7.9</td>
<td>25.5</td>
<td>4.26 (3.51–5.18)</td>
<td>19.1% (16.8–21.7)</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>7.4</td>
<td>16.2</td>
<td>2.67 (2.36–3.02)</td>
<td>10.1% (8.9–11.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>F</td>
<td>28.3</td>
<td>53.0</td>
<td>2.95 (2.57–3.39)</td>
<td>35.8% (32.1–39.6)</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>19.7</td>
<td>34.6</td>
<td>2.32 (2.12–2.53)</td>
<td>19.5% (17.7–21.5)</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>F</td>
<td>33.3</td>
<td>45.6</td>
<td>2.26 (1.90–2.68)</td>
<td>35.9% (28.9–43.6)</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>33.3</td>
<td>46.5</td>
<td>2.24 (2.03–2.47)</td>
<td>32.1% (28.0–36.5)</td>
</tr>
<tr>
<td>Psychosocial index</td>
<td>F</td>
<td>–</td>
<td>–</td>
<td>3.49 (2.41–5.04)</td>
<td>40.0% (28.6–52.6)</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>–</td>
<td>–</td>
<td>2.58 (2.11–3.14)</td>
<td>25.3% (18.2–34.0)</td>
</tr>
<tr>
<td>Fruits/veg</td>
<td>F</td>
<td>50.3</td>
<td>39.4</td>
<td>0.58 (0.48–0.71)</td>
<td>17.8% (12.9–24.1)</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>39.6</td>
<td>34.7</td>
<td>0.74 (0.66–0.81)</td>
<td>10.3% (6.9–15.2)</td>
</tr>
<tr>
<td>Exercise</td>
<td>F</td>
<td>16.5</td>
<td>9.3</td>
<td>0.48 (0.39–0.59)</td>
<td>37.3% (26.1–50.0)</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>20.3</td>
<td>15.8</td>
<td>0.77 (0.69–0.85)</td>
<td>22.9% (16.9–30.2)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>F</td>
<td>11.2</td>
<td>6.3</td>
<td>0.41 (0.32–0.53)</td>
<td>46.9% (34.3–60.0)</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>29.1</td>
<td>29.6</td>
<td>0.88 (0.81–0.96)</td>
<td>10.5% (6.1–17.5)</td>
</tr>
<tr>
<td>ApoB/ApoA1 ratio</td>
<td>F</td>
<td>14.1</td>
<td>27.0</td>
<td>4.42 (3.43–5.70)</td>
<td>52.1% (44.0–60.2)</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>21.9</td>
<td>35.5</td>
<td>3.76 (3.23–4.38)</td>
<td>53.8% (48.3–59.2)</td>
</tr>
</tbody>
</table>
CRP in the Prediction of Cardiovascular Disease in Women
Metabolic syndrome
Must have 3 of 5 criteria in women*

- Waist circumference >35 inches
- Fasting triglycerides >150 mg/dl
- HDL cholesterol <50 mg/dl
- Hypertension (systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg or use of antihypertensive drug therapy)
- Fasting glucose measurement ≥ 100 mg/dl

*NCEP ATP III panel
Effect of CRP and Metabolic Syndrome on Cardiovascular Mortality in Women
Effect of Weight Loss on CRP Concentration in Obese Healthy Women

- 83 women (mean BMI 33.8) placed on low fat diet for 12 weeks
- Baseline CRP positively associated with BMI (p=0.01)
- CRP reduced by 25% (p<0.001)
- Average weight loss 7.9 kg, associated with change in CRP
- Change in CRP correlated with change in TC (p=0.03) but not changes in LDL, HDL or glucose
- At 12 weeks, CRP concentration highly correlated with TG (p=0.009) but not with other lipids or glucose
Female-Specific Risk Factors

• Endometriosis
• Polycystic Ovary Syndrome (PCOS)
• Pregnancy: A “Natural” Stress Test
  – Gestational Diabetes
  – Pre-eclampsia
• Menopause
Incidence Rate of MI, Angina and CABG/PTCI across Age in Years

Mu et al. Circ Cardiovasc Qual Outcomes. 2016;9:00-00.
Relative Risk of Maternal Cardiovascular Disease in Studies of Hypertensive Disorders of Pregnancy

<table>
<thead>
<tr>
<th>First Author, Year (Reference No.)</th>
<th>Relative Risk (95% CI)</th>
<th>Mean or Median Years of Follow-up</th>
<th>Caption Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jonsdottir, 1995 (67)</td>
<td>1.90 (1.02, 3.52)</td>
<td>Unknown</td>
<td>a</td>
</tr>
<tr>
<td>Hannaford, 1997 (66)</td>
<td>1.65 (1.26, 2.16)</td>
<td>Up to 26</td>
<td>b</td>
</tr>
<tr>
<td>Irgens, 2001 (20)</td>
<td>3.61 (0.76, 17.18)</td>
<td>13</td>
<td>c, d</td>
</tr>
<tr>
<td>Smith, 2001 (34)</td>
<td>2.10 (1.60, 2.60)</td>
<td>15–19</td>
<td>b</td>
</tr>
<tr>
<td>Kestenbaum, 2003 (19)</td>
<td>2.55 (1.70, 3.83)</td>
<td>8</td>
<td>c, d</td>
</tr>
<tr>
<td>Wilson, 2003 (64)</td>
<td>1.95 (0.90, 4.22)</td>
<td>Unknown</td>
<td>a</td>
</tr>
<tr>
<td>Funai, 2005 (65)</td>
<td>3.01 (2.18, 4.33)</td>
<td>30</td>
<td>e</td>
</tr>
<tr>
<td>Wikstrom, 2005 (21)</td>
<td>2.21 (1.56, 3.31)</td>
<td>19–28</td>
<td>b, d</td>
</tr>
<tr>
<td>Lykke, 2009 (63)</td>
<td>1.82 (1.65, 2.00)</td>
<td>15</td>
<td>b</td>
</tr>
<tr>
<td>Mongraw-Chaffin, 2010 (39)</td>
<td>2.73 (1.78, 4.18)</td>
<td>37</td>
<td>e</td>
</tr>
<tr>
<td>Skjaerven, 2012 (68)</td>
<td>1.90 (1.60, 2.20)</td>
<td>25</td>
<td>e</td>
</tr>
</tbody>
</table>

Incidence of CHD
Relation to Menopause Status

Nurses’ Health Study

- 1976 with 121,964 women ages 30 to 55 free of CAD at enrollment
- 2 year follow up 92.7% responses
- E2 users vs. nonusers age adjusted relative risk
  - 0.5 in those who’d ever used E2
  - 0.3 in current users
  - Adjusted for tobacco, hypertension, DM, cholesterol, family history

10 year follow up

- Current E2 users 0.56 RR
- No effect on duration of use independent of age
- Nonsignificant trend toward decreasing benefits of E2 with increasing age

Framingham Heart Study

• 1234 women ages 50 -83

• Despite favorable lipid profiles, women reporting E2 use had 50% elevated risk in CV morbidity; however, if angina excluded, this was nonsignificant

• ↑ MI mortality risk- particularly among smokers

• Nonsmoker E2 use was only associated with increased risk of stroke

*Pts on high dose E2 (>1.25 mg/day)
Heart Estrogen/Progestin Replacement Study (HERS)

Women’s Health Initiative
Benefits and Risks of 2 Hormone Therapies

A CEE-MPA Trial

Intergroup Difference in No. of Events per 1000 Women over 5 Yr

Benefits & Risks

- Coronary Heart Disease: 2.5
- Stroke: 2.5
- Deep-Vein Thrombosis: 5.0
- Breast Cancer: 3.0
- Colorectal Cancer: -0.5
- All Cancers: -0.5
- All Fractures: -12.0
- Death from Any Cause: -5.0
- Diabetes: -5.5

B CEE-Alone Trial

Intergroup Difference in No. of Events per 1000 Women over 5 Yr

Benefits & Risks

- Coronary Heart Disease: -5.5
- Stroke: -0.5
- Deep-Vein Thrombosis: 2.5
- Breast Cancer: -2.5
- Colorectal Cancer: -1.5
- All Cancers: -4.0
- All Fractures: -8.0
- Death from Any Cause: -5.5
- Diabetes: -13.0
Danish Osteoporosis Prevention Study
2016 peri menopausal women randomized

Assigned (1006)
- 502 HT
- 504 placebo

Choice (1010)
- 221 HT

Vascular Effects of Early versus Late Postmenopausal Treatment with Estradiol (ELITE)

Effectiveness Based Guidelines for the Prevention of Cardiovascular Disease in Women – 2011 Update
Focus on Cardiovascular Care for Women

Summary

• Research Initiatives
  – Investigating sex differences in heart failure presentations
  – Catheterization lab to be poised to conduct trials of microvascular disease

• Multidisciplinary Clinic

• Educational Mission