Sex Differences in the Heart

Whitehead Institute Seminar Series: Sex Differences in Health and Disease
March 2, 2020

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Department of Medicine, Brigham and Women’s Hospital
• Heart disease in women
• The estrogen story
• Sex differences in heart failure
• Heart disease in women
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• Sex differences in heart failure
A closer look at the heart

ARTERIES

PUMP

VALVES

RHYTHM
Sex differences in cardiovascular disease

**ARTERIES**
- Lower incidence of CAD and ACS
- Microvascular disease common

**VALVES**
- Present later in life
- Tricuspid regurgitation more common

**RHYTHM**
- Atrial fibrillation less common, but higher stroke rate

**PUMP**
- Non-ischemic etiology
- Preserved LVEF
Circulating biomarkers differ in men and women.
• Heart disease in women
• The estrogen story
• Sex differences in heart failure
Heart disease rises precipitously post-menopause

AJMC 2000: 6(14 Suppl):S746-60
Estrogen signaling
Estrogen and the cardiovascular system

**ATHEROSCLEROSIS**
- ↓ LDL oxidation
- ↓ LDL binding
- ↑ BP
- ↓ oxidative damage
- ↓ VSMC proliferation

**VASOREACTIVITY**
- ↑ vasodilation
- ↑ nitric oxide
- ↓ endothelin
- ↑ COX2
- ↓ neuroendocrine response
- ↓ VSMC proliferation

**THROMBOSIS**
- ↑ coagulation factors
- ↓ platelet aggregation

**ARRHYTHMIAS**
- QT prolongation

JACC 2009; 53:221-31
Hormone therapy reduced heart disease in observational studies

**POSTMENOPAUSAL ESTROGEN THERAPY AND CARDIOVASCULAR DISEASE**

**Ten-Year Follow-up from the Nurses’ Health Study**

Meir J. Stampfer, M.D., Graham A. Colditz, M.B., B.S., Walter C. Willett, M.D., JoAnn E. Manson, M.D., Bernard Rosner, Ph.D., Frank E. Speizer, M.D., and Charles H. Hennekens, M.D.

<table>
<thead>
<tr>
<th>Group</th>
<th>Major Coronary Disease RR (95% CI)</th>
<th>Fatal CV Disease RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current HRT use, adj for age</td>
<td>0.51 (0.37-0.70)</td>
<td>0.48 (0.31-0.74)</td>
</tr>
<tr>
<td>Current HRT use, adj for age and RFs</td>
<td>0.56 (0.40-0.80)</td>
<td>0.61 (0.37-1.00)</td>
</tr>
</tbody>
</table>

NEJM 1991; 325:756-62
Hormone therapy increased CV events in randomized controlled trials!

- **Estrogen + progestin in healthy postmenopausal women**
  - Cumulative hazard of CHD
  - HR 1.24 (0.97-1.60)

- **Estrogen in postmenopausal women with hysterectomy**
  - Cumulative hazard of stroke
  - HR 1.39 (1.10-1.77)

N Engl J Med 2003;349:523-34  
JAMA 2004; 291(14):1701-12
Menopause and hormone status influence circulating biomarkers

1. Women
2. Pre-menopausal women
3. Post-menopausal women
4. Women not on HRT
5. Women on HRT
Estrogen and the cardiovascular system

A Estrogen regulation of nitric oxide signaling in young healthy females

B Estrogen regulation of nitric oxide signaling in old and diseased females
• Heart disease in women
• The estrogen story
• Sex differences in heart failure
Sex differences in heart failure
Two types of heart failure

- **Reduced ejection fraction**: Weakened ventricle - less blood is pumped out.

- **Preserved ejection fraction**: Stiff ventricle walls - less blood enters the ventricles.
Myocardial remodeling in HFrEF vs HFpEF
Lifetime risk of developing HF is similar in men and women

Circulation 2002:106;3068-3072
HFpEF is more prevalent in women than men
Women develop greater cardiac hypertrophy with age than men.
Obesity associates with risk of HFpEF, especially in women.
Women develop HFpEF at lower burden of comorbidities

JAMA Cardiol 2020;5(1):30-37
Cardiopulmonary Exercise Test (CPET)

- Pulmonary Artery Catheter
- Face Mask
- Radial Artery Catheter
- Registered Nurse
- Exercise Physiologist
- Supervising Physician
- Cycle Ergometer
- ECG Lead
- Metabolic Cart and Pressure Display

Circulation 2013; 127:1157-1164
Exercise responses in men and women with HFpEF

<table>
<thead>
<tr>
<th>Lungs</th>
<th>Total VO₂</th>
<th>Total work</th>
<th>MVV</th>
<th>ΔPAP/ΔCO</th>
<th>ΔRVEF</th>
<th>ΔSV</th>
<th>ΔHR</th>
<th>ΔCO</th>
<th>ΔPCWP/ΔCO</th>
<th>ΔLVEF</th>
<th>ΔBP</th>
<th>Hb</th>
<th>ΔC(a-ve)O₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart, Blood, Vasculature</td>
<td>Difference Between Men and Women, %</td>
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JAMA Cardiol 2020;5(1):30-37
Women with HFpEF have lower quality of life
…but better survival
Sex differences in heart failure

- Significant comorbidity burden
- Hypertensive disorders of pregnancy
- Emotional stress
- Breast cancer treatment
- Greater vascular stiffness
- Greater LV concentric remodelling

**Predominant endothelial inflammation-coronary microvascular dysfunction**

**Phenotypes**
- HFrEF
- Takotsubo CM
- PPCM

**Prognosis**
- Greater exercise limitation
- Lower QoL
- Better survival

**Myocardial infarction predominates as a HF risk factor**

- Younger age at presentation
- Obesity promotes development of HFrEF rather than HFrEF
- Alcohol and illicit drug use more common exposures

**Predominant macrovascular disease, myocyte necrosis and scar formation**

**Phenotypes**
- HFrEF

**Prognosis**
- Higher mortality
- Better QoL

Eur Heart Journal
<table>
<thead>
<tr>
<th>Conclusion</th>
<th>Details</th>
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<tbody>
<tr>
<td>Heart disease is different in men and women</td>
<td>Sex differences in biomarkers: biological pathways differentially activated in men &amp; women</td>
</tr>
<tr>
<td>CVD risk increases after menopause but estrogen does not reduce risk</td>
<td>Menopause and hormone status may affect certain biological pathways but not all</td>
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<tr>
<td>Heart failure with preserved ejection fraction is more common in women</td>
<td>Women are more susceptible to the deleterious effects of HTN, obesity and diabetes.</td>
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<td>Heart disease is not just a man’s disease = leading cause of death in women</td>
<td>We need more research in women from animal studies to randomized trials!</td>
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</table>
Thank you!

Jennifer Ho
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Ho Lab 2018