Mechanisms Underlying Cardiac Aging in Women

Cemal Ozemek, PhD
Geriatric Medicine
Ejection Fraction in CHF

Men

- Normal: 42%
- Mild: 27%
- Mod/Sev: 31%

Women

- Normal: 67%
- Mild: 23%
- Mod/Sev: 10%

Kitzman et al. Am J Cardiol 2001
Aging?
Pathophysiologic “Syndrome” of HF

- Pulmonary mismatching
- Inefficient ventilation & DOE
- Renal hypoperfusion
- Myocardial dysfunction
- Increased afterload
- Arterial vasoconstriction
- Muscle hypoperfusion
- Skeletal muscle dysfunction
- Exercise intolerance

Brubaker
Ventricular-Vascular Coupling

Chantler and Lakatta, *Front Phys* 2012

[Graphs showing the relationship between LV stiffness and vascular stiffness for different age groups and genders.]
Mitral Inflow Pattern
Tissue Doppler

$E/e' = \frac{\text{Early mitral inflow velocity}}{\text{Early tissue velocity}}$
LV Diastolic Function with Age/Gender

- Predictors of impaired LV relaxation
  - Age ≥50 years & female gender
Aging

LV Diastolic + Arterial Dysfunction

↓ $E_2$

HFpEF
Cardiac Tissue

OVX → ↑ E/e’

OVX + E2 → ↔ E/e’

SHAM → E/e’

NOS Uncoupling
Oxidative Stress & LV Diastolic Function

• **Subjects**
  - Premenopausal (n=14, 18-40 yr)
  - Postmenopausal (n=23, 45-70 yr)
  - Healthy with no CVD risk factors
  - No oral contraceptive or hormone replacement therapy

• **Experimental design**
  - Saline vs. Ascorbic acid (60mg/kg fat free mass) infusions (20 min)
    - LV Diastolic Function
    - Carotid artery compliance
    - Total antioxidant status
# Oxidative Stress & LV Diastolic Function

<table>
<thead>
<tr>
<th>Mitral valve in flow</th>
<th>Premenopausal (n=14)</th>
<th>Postmenopausal (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saline</td>
<td>Ascorbic Acid</td>
</tr>
<tr>
<td>E (cm/s)</td>
<td>85 ± 9</td>
<td>81 ± 8</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>47 ± 12</td>
<td>48 ± 10</td>
</tr>
<tr>
<td>E/A</td>
<td>1.65 (1.53-2.30)</td>
<td>1.65 (1.46-1.91)</td>
</tr>
</tbody>
</table>

Ozemek et al. *Menopause*. Under review
LV Diastolic Function & Carotid Artery Compliance

Ozemek et al. Menopause. Under review
Aging

LV Diastolic + Artery Dysfunction

Uncoupled NOS

↓ E2

↓ NO

ROS

Observational Studies
Improved LV Diastolic function

Climara 50
Alternative Therapies

Postmenopausal women (n=6)
- Placebo
- BH4

OVX Animal Models

O2 → BH4 → L-Citrulline
L-arginine → eNOS → NO

NADPH

Graph:

- EA: Vascular Stiffness
- ELV: Ventricular Stiffness

BH4 vs Placebo
Mitochondria Targeted Antioxidants in CVD

- Improved endothelial function
- Improved LV diastolic function
- Improved structural characteristics (animal)

*No studies in menopause*
Aging

Menopause

BH4

CoQ

E2

?↑Arterial Stiffness

↓Nitric Oxide

↑Risk of HFpEF

↑ROS

↓BH4

Uncoupled NOS

↑Impaired VV-Coupling

↓Impaired
diastolic function

↓SERCA Calcium Reuptake

E2

BH4

CoQ

??
Thank You