HFPEF-how is it different from HFREF and how do we treat?

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Diastolic and Systolic Heart Failure

- **Historical Perspective:**
  - “those forms of cardiac insufficiency
    - which are due to inadequate diastolic
    - filling of the heart (hypodiastolic failure)
  - [and] the far more common ones in which
    - heart fills adequately but does not empty
    - to the normal extent (hyposystolic failure)”

Diastolic Heart Failure

- Diastolic Heart Failure:

  Pathophysiologic definition:
  - Brutsaert et al (1993)
  - “A condition resulting from an increased resistance to filling of one or both ventricles leading to symptoms of congestion due to an inappropriate shift of the diastolic pressure volume relation”
Diastolic Heart Failure

- Diastolic Heart Failure - contemporary clinical definitions:
  - "A clinical syndrome characterized by the symptoms and signs of heart failure, a preserved ejection fraction, and abnormal diastolic function."

- Other clinical definitions:
  - "Heart failure with preserved systolic function"
  - "Heart failure with normal or near normal ejection fraction"

Risk factors
- Older age
- Female gender
- African Americans
- Hypertension
- Diabetes
- Obesity
- Ischemic heart disease
Diastolic Heart Failure

Prevalence – Echocardiographic cross-sectional population studies

- Male: 2.7-6.6 %
- Female: 1.7-9.5 %
- All: 2.2-8.8 %

Adapted from Hogg.K et al JACC,2004,43,317

Systolic Vs Diastolic Heart Failure

- ADHERE – All enrolled discharges

<table>
<thead>
<tr>
<th>Profile</th>
<th>SHF</th>
<th>DHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>(59,523)</td>
<td>(50,497)</td>
<td></td>
</tr>
<tr>
<td>EF</td>
<td>&lt;40%</td>
<td>&gt;40%</td>
</tr>
<tr>
<td>Age</td>
<td>69.9</td>
<td>74.2*</td>
</tr>
<tr>
<td>Female</td>
<td>39%</td>
<td>62.2 %*</td>
</tr>
<tr>
<td>CAD</td>
<td>63 %</td>
<td>54%*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>42 %</td>
<td>46 % *</td>
</tr>
<tr>
<td>AF</td>
<td>29%</td>
<td>33 % *</td>
</tr>
<tr>
<td>BNP</td>
<td>1486</td>
<td>925 *</td>
</tr>
</tbody>
</table>

* < 0.0001
Diastolic Heart Failure-Remodeling

- Ventricular hypertrophy, usually concentric
- Increased ventricular mass
- Increased ventricular wall thickness
- Little or no increase in the cavity size
- Increased mass/cavity ratio
- Decreased wall stress
- Maintained ejection fraction
- Little or no change in ventricular shape
  - Mechanical dyssynchrony with or without electrical dyssynchrony present in approx 1/3rd

Systolic Heart Failure-Remodeling

- Usually eccentric hypertrophy
- Disproportionate increase in ventricular cavity size
- Increased ventricular mass
- Cavity / mass ratio increased
- Wall thickness – decreased or unchanged
- Increased wall stress
- Reduced ejection fraction
- Altered ventricular shape and geometry
- Frequent mechanical dyssynchrony with or without electrical dyssynchrony
### Diastolic and Systolic Heart Failure

- **Controls**
- **DHF**
- **SHF**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Controls</th>
<th>DHF</th>
<th>SHF</th>
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</thead>
<tbody>
<tr>
<td>LVEDV</td>
<td>102</td>
<td>87</td>
<td>192</td>
</tr>
<tr>
<td>LVESV</td>
<td>46</td>
<td>37</td>
<td>137</td>
</tr>
<tr>
<td>LVEF</td>
<td>54</td>
<td>60</td>
<td>31</td>
</tr>
<tr>
<td>LVM</td>
<td>125</td>
<td>160</td>
<td>230</td>
</tr>
<tr>
<td>LVM/V</td>
<td>1.49</td>
<td>2.12</td>
<td>1.22</td>
</tr>
</tbody>
</table>

(Kitzman et al, JAMA, 2002)
**Diastolic and Systolic Heart Failure**

- Myocardial Structure and Function Differ in Systolic and Diastolic Heart Failure
- Heerbeek L v et al; Circulation. 2006; 113:1966-1973
- DHF | SHF | P
- MyD | 20.3 | 15.1 | <0.001
- ( microM)
- CVF | + | + | NS
- MFD % | 46 | 36 | <0.001

- MyD= myocyte diameter; CVF= collagen volume fraction; MFD = myofibrillar density
## Diastolic and Systolic Heart Failure

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<thead>
<tr>
<th></th>
<th>SHF</th>
<th>DHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocyte</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>hypertrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>apoptosis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>necrosis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fibrosis</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Ca regulation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MMPs/TIMPs</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Collagen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cross-links</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Titin isoforms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2BA/ N2B</td>
<td>+</td>
<td>-</td>
</tr>
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</table>

## Does Diastolic Heart Failure Evolve to Systolic Heart Failure

- LVlDVI LVEDP Stiff-Mod LVEF
- (ml/m2) (mmHg) kn/m2 (%)
- Init 68+-9 14+-3 3.4+-0.6 67+-3
- End 76+-8 26+-2 * 6.3 +-0.9* 60+-4
- n=10 pts, follow up=64+-9 months
- No CAD initial or end study
Diastolic Heart Failure
Hemodynamic Abnormalities

Principal mechanism – LV diastolic dysfunction
- Increased LVDP $\rightarrow$ $\uparrow$ LAP $\uparrow$ PVP
- Post capillary pulmonary hypertension
- RV failure $\rightarrow$ $\uparrow$ RAP
- Impaired ventricular filling
- Decreased SV and CO
Systolic Heart Failure
Hemodynamic Consequences

- Reduced Ejection Fraction:
- Decreased FSV-decreased Cardiac output.
- Increased ESV and EDV: increased LVDP, LAP, PCWP
- Post capillary pulmonary hypertension:
  Secondary right ventricular failure:
  Increased systemic venous pressure

Systolic Vs Diastolic Heart Failure
Neurohormonal dysfunction

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>SHF</th>
<th>DHF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF</td>
<td>54%</td>
<td>31%</td>
<td>60%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NE Pg/ml</td>
<td>169</td>
<td>287</td>
<td>306</td>
<td>P= .007</td>
</tr>
<tr>
<td>BNP Pg/ml</td>
<td>3</td>
<td>28</td>
<td>56</td>
<td>P= .02,.001</td>
</tr>
</tbody>
</table>

(Kitzman D.W et al JAMA, 2002)
Diastolic Heart Failure

- **Prognosis:**
- **Asymptomatic diastolic dysfunction:** natural history not adequately studied
- **Echocardiographic and Doppler studies** (Redfield et al, JAMA, 2003)
- **Risk of all cause mortality:**
  - Mild dysfunction - 8.3 fold increase
  - Moderate to severe dysfunction – 10.2 fold increase

The Charm-Preserved Trial

- **Candessartan** (n=1514)  **Placebo** (n=1509)

<table>
<thead>
<tr>
<th>NYHA Class</th>
<th>Candessartan</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>II</td>
<td>61.5%</td>
<td>60.0%</td>
</tr>
<tr>
<td>III</td>
<td>36.7%</td>
<td>38.7%</td>
</tr>
<tr>
<td>IV</td>
<td>1.8%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

Mean (SD) LVEF %

<table>
<thead>
<tr>
<th>LVEF %</th>
<th>Candessartan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>41-49%</td>
<td>35.4%</td>
<td>35.5%</td>
</tr>
<tr>
<td>50-59%</td>
<td>36%</td>
<td>33.9%</td>
</tr>
<tr>
<td>&gt;60%</td>
<td>28.6%</td>
<td>30.6%</td>
</tr>
</tbody>
</table>
The Charm-Preserved Trial

- Candesartan          Placebo
- ( n=1514 )            ( 1509 )
Cardiovascular Death
11.2%                   11.3%
Annual Mortality Rate
3.8%                     3.8%

Distolic and Systolic Heart Failure

- Mortality and Morbidity
- DHF          SHF
- EF %                             60      25
- Mort%                       2      3
- In-hosp             6      11
- 2-mo                        11     16
- 6-mo
- Readmission
  +
  Mortality%                        53     56

( Adapted from :Danciu SC et al; AJC: 2006; 97, 256-259 )
Diastolic Heart failure

- Retrospective-Duke data base
- No. of patients-1941
  - EF % 50
  - Years 1995-2004
  - Mortality 548 patients (28%)
  - SCD 40/548 (7.3%)

Diastolic Heart Failure

- Sudden Cardiac Death
  - Post-hoc analysis (Peace) trial
  - No -8290, LVEF > 40%
  - SCD occurred in 1.5% of patients during a median follow-up of 4.8 years. (mean EF 58%)
  - The independent predictors of SCD –
    - Digitalis use – HR-2.58
    - Diuretic use – HR – 2.1
    - LVEF < 50% - HR-2.08
    - Current angina-HR-1.51
Beta-blockers in DHF

- Swedish Doppler-echocardiographic study (SWEDIC)
- 113 patients randomized to receive carvedilol or placebo
- E/A ratio improved with carvedilol

Beta-blockers in DHF

- Study of Effects of Nevibolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS)
- JACC, 2009; 53:2150-8
- 2128 patients 70 years or older randomized, both SHF and DHF included
- There was an indication of decreased mortality and rate of hospital admissions
Diastolic Heart Failure

- **PEP-CHF**

- The perindopil in elderly people with chronic heart failure (PEP-CHF) study
- Decreases morbidity, no decrease in mortality
- Cleland JGF et al, Europ. Heart J, 2006, 27;238-2345

The Charm Preserved Trial

- **Candesartan** Placebo
- (n=1514) (n=1509)

Cardiovascular death or hospital admission for CHF: 22.0% p=0.051 24.3%
Cardiovascular death:
11.2% p=.635 11.3%
Hospital admission for CHF:
15.9% p=.047 18.3%
Diastolic Heart Failure

- Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE)
- Randomized, double-blind, placebo control parallel assignment efficacy study
- NYHA Class II and III patients
- Irbesartan 300mg or placebo
- Patients no: 4133
- Primary endpoint: death from any cause
- CV hospitalization
- Secondary endpoints: all-cause mortality;
  - CV death; composite of CV death or non-fatal MI or stroke; HF death or hospitalization; changes in functional status; quality of life; NYHA class; global change score; changes in BNP.
Aldosterone antagonist in DHF

- Thirty hypertensive patients with diastolic heat failure were randomized to placebo
- or 25 mg of spironolactone: diastolic function improved with spironolactone.

Aldosterone antagonist in DHF

- Two large ongoing randomized trials:
  - Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-DHF)
  - Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT).

Sildenafil in DHF

- A randomized trial: 22 patients received placebo and 22 patients received sildenafil 50 mg three times daily.
- All patients had mixed PAH
- PCWP, RAP, PVR decreased,
- CO increased at 6 months
- SVR and MAP remain unchanged
- Left and right ventricular function improved
Statin in Diastolic Heart Failure

- Statin Therapy May Be Associated With Lower Mortality in Patients With Diastolic Heart Failure, A preliminary Report.
- Fukuta H, Sane DC, Brucks S, Little WC
- Circulation, 2005; 112: 357-363

Diastolic heart failure

- New potential therapies:
  - Modulation of collagen cross-links
  - Modulation of Titin isoforms
  - Modulation of MMP/TIMP
  - Reduction of matrix fibrosis:
    - Chymase antagonists
    - TGF-beta
  - Improved relaxation:
    - Phospholamban inhibition
    - D-ribose
    - Levosimendan (calcium sensitiser)
Thank You