Multiple Etiologies and Approaches to HFpEF

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No disclosures
HFpEF (569 refs)

568. Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban Baltimore community: the role of atrial remodeling/dysfunction.
PMID: 17222731 Free Article
Similar articles

569. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction.
Borlaug BA, Melenovsky V, Russell SD, Kessler K, Pacak K, Becker LC, Kass DA.
PMID: 17088459 Free Article
Similar articles
HFpEF

Patients with symptoms that remind us of this other disease where the ejection fraction is low because the heart dilates and is weak - BUT – in these folks the EF is fine.

Go figure.
What’s in a name:

HFpEF

Heart is a major problem

Heart is a minor problem

Heart’s fine
It’s diastole’s fault!

Relaxation
And filling
As opposed to the *Systole Hotel*
The Classical Perspective: Diastolic Heart Failure

Aurigemma et al. *Circulation* 2006

Zile et al. *Circulation* 2015
You gotta problem with this? (you should)

• Diastolic dysfunction is extremely common in elderly with similar co-morbidities yet no HF. (*many studies*)
• Diastolic disease is modest in many HFpEF patients, and not a good predictor of outcome (*whereas LVH, PAH, and elevated filling pressures are*).
• Left atrial size (big) and atrial contractile function (weak) seem more common in HFpEF. (*Melanovský et al, JACC 2007*)
• Improved exertional capacity from endurance training occurs without evidence of improved systolic or diastolic function (*Pandey et al, Circ-HF 2015*).
There’s much more than diastolic function at work: Ventricular-Arterial stiffening on cardiac response to exercise (handgrip)

Systole may be normal at rest, but reserve during exercise is blunted

Borlaug et al. JACC 2010; 56:845-54.
Chronotropic and Vasodilator Insufficiency

Borlaug et al. Circulation 2006;114:2138-47

- **Heart Rate (bpm)**
  - Time (seconds)
  - Control
  - HFpEF

- **Peak Oxygen Uptake (mL O₂ min⁻¹ kg⁻¹)**
  - Change in Heart Rate (bpm)
  - Correlation: r=0.66, p<0.0001

- **Peak Oxygen Uptake (mL O₂ min⁻¹ kg⁻¹)**
  - Change in SVR (dynes sec⁻¹ cm⁻⁵)
  - Correlation: r=0.52, p<0.002
Obesity, Sarcopenia, and Metabolic Defects with HFpEF

**Healthy Controls**
- Reduced Type 1 fiber (mito rich, power, slow)
- Reduced capillary to fiber ratio
- Impaired skeletal muscle metabolism (NMR)

Kitzman et al, AJP 2014
Bhella et al. Eur J of Heart Fail 2011
Fat infiltration in skeletal muscle – tasty – but not necessarily good for you

Increase in skeletal muscle fat impedes metabolic function, contributes to insulin resistance and myokine defects, and contributes to nutrient supply/demand imbalance.

HFpEF: The “straw that breaks the camel’s back” - disease
But are there really good animal models?

- Pressure overload
- Diet-obesity/HTN
- ZSF-1 rat
- MI+HTN
- AII/renal vascular HTN
- Any mouse that has diastolic dysfunction and EF>50%
How do we treat it?

- Diuretics
- Treat hypertension
- Treat atrial arrhythmias
- Targeting RAAS has not been effective
One of the best treatments – move to Russia

TOPCAT – Aldosterone Trial – Outcomes by site
What might be potential targets – with at least some heart effects?

Evolution of an inflammatory/NOS-opathic hypothesis

Sharma and Kass (Circ Res 2014)
New Stuff:

• Entresto: (LCZ 696, AT2 + Neprilysin Blocker)
  PARAGON-HF
• Udenafil (PDE5 inhibitor)
  ULTIMATE-HFpEF
• Vericiguat (sGC stimulator)
  SOCRATES-PRESERVED
• Perhexiline (reduces FFA metabolism)
• Exercise
• Devices: Vagal stimulation / LA monitors
• PDE9 inhibitor?
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

FDA News Release

FDA approves new drug to treat heart failure

For Immediate Release

July 7, 2015

The U.S. Food and Drug Administration today approved Entresto (sacubitril/valsartan) tablets for the treatment of heart failure. The drug has been shown to reduce the rate of cardiovascular death and hospitalization related to heart failure.

natriuretic peptide system  
pro-BNP

heart failure

renin-angiotensin system  
angiotensinogen (liver secretion)
Cyclic GMP and Protein Kinase G signaling is blunted in HFpEF

AS – Aortic Stenosis

Van Heerebeek et al, Circulation 2012
PDE9a KO mice are protected against Sustained Pressure-overload (Trans-aortic constriction – TAC)

But only PDE9 works if NOS function is suppressed

PDE9A Protein Expression is increased in Human DCM and particularly HFpEF

Lee et al, Nature 2015: 519, 472–476
"What's in a name? That which we call a disease by any other name would still make us just as sick."

Romeo and Juliet (Out-take from Doctor Scene II, ii, 1-2)

• Diastolic Heart Failure (DHF)
• Heart Failure with normal EF (HFnEF)
• Heart Failure with preserved EF (HFpEF)
• EXIT (exertional intolerance)
• CAPRI-Me Syndrome
CAPRI-Me Syndrome

Cardiovascular
Pulmonary
Renal
Insufficiency
Metabolic Defects
Role of collagen vs Titin in myocardial stiffening in “HFpEF”

Zile et al. Circulation 2015;131:1247
Wireless Pulmonary Artery Pressure Monitoring Guides Management to Reduce Decompensation in Heart Failure With Preserved Ejection Fraction

Philip B. Adamson, MD; William T. Abraham, MD; Robert C. Bourge, MD; Maria Rosa Costanzo, MD; Ayesha Hasan, MD; Chethan Yadav; John Henderson, BS; Pam Cowart, RN; Lynne Warner Stevenson, MD
Atrial Dilation and dysfunction: A discriminating feature

Melenovsky et al. JACC 2007;49:198-207
### Culpable Common Co-morbidities

<table>
<thead>
<tr>
<th>COMORBIDITY</th>
<th>BIDIRECTIONAL IMPACT ON DISEASE PROGRESSION</th>
<th>HEART FAILURE SPECIFICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>Inflammation; hypoxia; parenchymal changes; airflow limitation, leading to pulmonary congestion; abnormal left ventricular (LV) diastolic filling; inhaled beta-agonist cardiovascular effects</td>
<td>More prevalent in preserved ejection fraction (HFrEF), compared to reduced (HFrEF) Higher mortality risk in HFpEF</td>
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<td>Elevated LV end-diastolic pressure and beta-blocker use may compromise lung function</td>
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<td>Anemia</td>
<td>Adverse LV remodeling; adverse cardiorenal effects; increased neurohormonal and inflammatory cytokines</td>
<td>More prevalent in HFpEF</td>
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<tr>
<td></td>
<td>Inflammation; hemodilution; renal dysfunction; metabolic abnormalities exacerbate</td>
<td>Similar increased risk for mortality in both groups</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Diabetic cardiomyopathy; mitochondrial dysfunction; abnormal calcium homeostasis; oxidative stress; renin-angiotensin-aldosterone system (RAAS) activation; atherosclerosis; coronary artery disease</td>
<td>More prevalent in HFpEF</td>
</tr>
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<td></td>
<td>Incident and worsening diabetes mellitus via sympathetic and RAAS activation</td>
<td>Similar increased risk for mortality in both groups</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>Sodium and fluid retention; anemia; inflammation; RAAS and sympathetic activation</td>
<td>Similar prevalence in both groups</td>
</tr>
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<td></td>
<td>Cardiorenal syndrome through low cardiac output; accelerated atherosclerosis; inflammation; increased venous pressure</td>
<td>Similar increased risk for mortality in both groups</td>
</tr>
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<td>Sleep-disordered breathing</td>
<td>Hypoxia; systemic inflammation; sympathetic activation; arrhythmias; hypertension (pulmonary and systemic); RV dysfunction; worsening congestion</td>
<td>Similar prevalence in both groups</td>
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<td>Rostral fluid movement may worsen pharyngeal obstruction; instability of ventilatory control system</td>
<td>Unknown mortality differential associated with HFpEF vs. HFrEF</td>
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<tr>
<td>Obesity</td>
<td>Inflammation; reduced physical activity and deconditioning; hypertension; metabolic syndrome; diabetes mellitus</td>
<td>More prevalent in HFpEF</td>
</tr>
<tr>
<td></td>
<td>Fatigue and dyspnea may limit activity; spectrum of metabolic disorders including nutritional deficiencies</td>
<td>Obesity paradox; potential for a U-shaped association with mortality</td>
</tr>
</tbody>
</table>

Mentz et al. *JACC 2014*:64
Enjoy Delicious Party Platter Menus for

Yom Kippur
Ramadan
Ash Wednesday
What about animal models?
HFpEF: The ultimate Gemischt disease