European Society of Cardiology
Heart Failure Annual Meeting

Highlights Session: Heart Failure with Preserved Ejection fraction

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Harvard University
Director, Noninvasive Cardiology
Brigham and Women’s Hospital
Boston, MA
DECLARATION OF INTEREST

- Consulting/Royalties/Owner/ Stockholder of a healthcare company
- Research contracts
HFpEF 2013

- Poor animal models
- Limited understanding of pathophysiology
- Heterogeneous Disorder
- Limited consensus in the HF community on etiology, diagnosis or treatment
- Can’t agree on a name
- Anecdote-Based Medicine
2012-2013: An Important year for HFpEF

- **ESC 2012**
  - PARAMOUNT (LCZ696) presented
  - ALDO-DHF (Spironolactone) Presented
- **ACC 2013**
  - RELAX (Sildenafil) presented
- **AHA 2013**
  - TOPCAT to be presented
- **Q4 2013 – PARAGON-HF outcomes trial starting**
Studies in HFpEF at ESC-HF

- Epidemiology
- Pathophysiology
- Diagnosis
- Cardiac Structure and Function
- Therapy

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EPIDEMIOLOGY
SURVIVAL IN AMBULATORY HEART FAILURE PATIENTS WITH PRESERVED EJECTION FRACTION, 1999-2011

Malcolm Arnold¹, Peter Liu², Marie-Hélène LeBlanc³, Jonathan Howlett⁴, Andrew Ignaszewski⁵, Annemarie Kaan⁵, Margaret Edmonds⁵, Marilyn Winkler⁶, Pamela Luehr⁷, Estrellita Estrella-Holder⁸ on behalf of all the nurses, dietitians, allied health care providers, and physicians in the CHFN

10,965 ambulatory HF patients with a documented LVEF

- Distribution of NYHA class similar in HFpEF and HFrEF
- Prevalence of CAD slightly lower in HFpEF
- Prelalence of atrial fibrillation slightly higher in HFpEF
Preserved LVEF did not confer benefit in survival.
Similar overall mortality in HFpEF and HFrEF patients
Findings are similar to previously reported by Olmstead County and Toronto registry, but different from clinical trials
Recent prior heart failure hospitalization is associated with increased risk of clinical events in patients with reduced and preserved ejection fraction in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM) trials

Natalie Bello¹, Akshay S. Desai¹, John J.V. McMurray², Christopher Granger³, Salim Yusuf⁴, Karl Swedberg⁵, Marc A. Pfeffer¹, Scott D. Solomon¹

- Risk of subsequent death or HF Hospitalization is greatest when the time from the last hospitalization is shortest
- These findings have implications for clinical trials
PATHOPHYSIOLOGY
Decreased left ventricular capacitance is associated with a titin isoform shift and reduced titin phosphorylation in a porcine model of early heart failure with preserved ejection fraction.

M. Schwarzl<sup>1</sup>, S. Seiler<sup>1</sup>, A. Alogna<sup>1</sup>, N. Hamdani<sup>2</sup>, W. Linke<sup>2</sup>, J. Verderber<sup>1</sup>, P. Steendijk<sup>3</sup>, BM. Pieske<sup>1</sup>, H. Post<sup>1</sup>

(1) Medical University Graz, Austria
(2) Ruhr University Bochum, Germany
(3) Leiden University Medical Center, Leiden, The Netherlands
Background & Methods

- **Aim**: to establish a risk-factor based animal model of heart failure with preserved ejection fraction.

- arterial hypertension
- dyslipidemia
- physical inactivity

- **bedside to bench**

- DOCA+salt
- „western-diet“
- physical inactivity
Results

- concentric LV hypertrophy
- Reduced Cardiac Output Reserve
- Decreased LV End-Diastolic Compliance
- Titin isoform shift and reduced titin phosphorylation
Conclusion

• **DOCA/western-diet treatment resulted in:**
  • concentric LV hypertrophy with
  • reduced cardiac output reserve and
  • decreased LV end-diastolic capacitance
  • titin-isoform-shift and reduced titin-phosphorylation

• **Enhancing titin-phosphorylation may improve LV dysfunction in HFpEF**
Fasting insulin resistance occurs in HFpEF and HFrEF

Non diabetic patients with HFrEF showed more severe insulin resistance

Insulin resistance observed in HFpEF as well as in HFrEF non diabetic patients

Insulin resistance within the physiologic range of insulin/glucose interaction is seen only in HFrEF but not in HFpEF
Galectin-3 Reflects Functional Capacity and Clinical Outcome in Heart Failure with Preserved Ejection Fraction (The Aldo-DHF Biomarker Sub-Study)


For the Aldo-DHF Investigators
Galectin-3 in Aldo-DHF:
Objective and Aims of the Biomarker Sub-Study

Aldosterone has been implicated in the pathogenesis of HFpEF via MR-receptor mediated myocardial fibrosis, hypertrophy, and stiffening of the left ventricle.

Edelmann F et al., Eur Heart J 2012;33:203-212

Galectin-3 is a marker of myocardial fibrosis, and it mediates aldosterone-induced vascular inflammation and fibrosis. In acutely decompensated patients with HFpEF high levels of Galectin-3 are associated with increased mortality.

de Boer RA et al., Curr Heart Fail Rep 2010;7:1-8
de Boer RA et al., Ann Med 2011;43:60-68

Aims of the Galectin-3 Sub-Study:

1) To investigate the clinical associations of galectin-3 in HFpEF.
2) To investigate the effect of chronic aldosterone receptor blockade on galectin-3 levels.
3) To investigate whether galectin-3 levels are predictive of treatment response to aldosterone receptor blockade in HFpEF.
4) To investigate whether time-dependent galectin-3 levels are related to clinical outcome in HFpEF.
# Galectin-3 and Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Galectin-3 ≤ 12.1ng/ml</th>
<th>Galectin-3 &gt; 12.1ng/ml</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>n=415</td>
<td>n=208</td>
<td>n=207</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female Gender</td>
<td>217 (52.3%)</td>
<td>100 (48.1%)</td>
<td>117 (56.5%)</td>
<td>0.085</td>
</tr>
<tr>
<td><strong>Medical History</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>382 (92.0%)</td>
<td>186 (89.4%)</td>
<td>196 (94.7%)</td>
<td>0.048</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>69 (16.6%)</td>
<td>28 (13.5%)</td>
<td>41 (19.8%)</td>
<td>0.083</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>21 (5.1%)</td>
<td>3 (1.4%)</td>
<td>18 (8.7%)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Signs and Symptoms of HF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA III</td>
<td>58 (14.0%)</td>
<td>20 (9.6%)</td>
<td>38 (18.4%)</td>
<td>0.010</td>
</tr>
<tr>
<td>Edema</td>
<td>164 (39.5%)</td>
<td>68 (32.7%)</td>
<td>96 (46.4%)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Cardiovascular Medication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-Inhibitor or ARB</td>
<td>321 (77.3%)</td>
<td>153 (73.6%)</td>
<td>168 (81.2%)</td>
<td>0.064</td>
</tr>
<tr>
<td>Beta-Blocker</td>
<td>299 (72.0%)</td>
<td>135 (64.9%)</td>
<td>164 (79.2%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diuretic</td>
<td>226 (54.5%)</td>
<td>94 (45.2%)</td>
<td>132 (63.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.8 (±1.2)</td>
<td>14.0 (±1.1)</td>
<td>13.7 (±1.3)</td>
<td>0.012</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>78.7 (±18.7)</td>
<td>84.7 (±17.2)</td>
<td>72.5 (±18.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)</td>
<td>159 (84-299)</td>
<td>140 (75-225)</td>
<td>192 (93-377)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
# Galectin-3 and Baseline Characteristics

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<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Galectin-3 ≤ 12.1ng/ml</th>
<th>Galectin-3 &gt; 12.1ng/ml</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%) , MW (±SD)</td>
<td>n=415</td>
<td>n=208</td>
<td>n=207</td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary Exercise Testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak VO₂ (mL/kg/min)</td>
<td>16.3 (±3.5)</td>
<td>16.9 (±3.2)</td>
<td>15.8 (±3.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>AT VO₂ (mL/kg/min)</td>
<td>11.6 (±3.2)</td>
<td>12.1 (±3.3)</td>
<td>11.1 (±3.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>VE/VCO₂ Slope</td>
<td>30.3 (±5.2)</td>
<td>29.7 (±5.3)</td>
<td>31.0 (±5.1)</td>
<td>0.016</td>
</tr>
<tr>
<td>6-Minute-Walk-Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distance (m)</td>
<td>530 (±87)</td>
<td>546 (±83)</td>
<td>514 (±88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>67.4 (±7.8)</td>
<td>67.0 (±7.7)</td>
<td>67.8 (±7.9)</td>
<td>0.268</td>
</tr>
<tr>
<td>LVMI, males (g/m²)</td>
<td>117.2 (±31.0)</td>
<td>120.4 (±33.8)</td>
<td>113.4 (±27.0)</td>
<td>0.112</td>
</tr>
<tr>
<td>LVMI, females (g/m²)</td>
<td>101.1 (±22.7)</td>
<td>100.6 (±24.1)</td>
<td>101.5 (±21.5)</td>
<td>0.770</td>
</tr>
<tr>
<td>LAVI (mL/m²)</td>
<td>28.1 (±8.5)</td>
<td>27.1 (±7.4)</td>
<td>29.1 (±9.3)</td>
<td>0.022</td>
</tr>
<tr>
<td>E/e’</td>
<td>12.8 (±4.1)</td>
<td>12.3 (±3.6)</td>
<td>13.2 (±4.4)</td>
<td>0.023</td>
</tr>
</tbody>
</table>
Clinical Correlates of Galectin-3

<table>
<thead>
<tr>
<th>Values are B-coefficients (95%-CI) by Regression</th>
<th>Model 1</th>
<th>P-value</th>
<th>Model 2</th>
<th>P-value</th>
<th>Model 3</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO$_2$ - mL/kg/min</td>
<td>-0.164</td>
<td>&lt;0.001</td>
<td>-0.098</td>
<td>0.023</td>
<td>-0.118</td>
<td>0.021</td>
</tr>
<tr>
<td></td>
<td>[-0.250;-0.078]</td>
<td></td>
<td>[-0.183;-0.014]</td>
<td></td>
<td>[-0.219;-0.018]</td>
<td></td>
</tr>
<tr>
<td>Six-Minute Walk Distance - m</td>
<td>-5.92</td>
<td>&lt;0.001</td>
<td>-3.95</td>
<td>&lt;0.001</td>
<td>-3.87</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>[-8.05;-3.80]</td>
<td></td>
<td>[-6.05;-1.85]</td>
<td></td>
<td>[-6.31;-1.43]</td>
<td></td>
</tr>
<tr>
<td>SF-36 Physical Functioning Scale</td>
<td>-1.40</td>
<td>&lt;0.001</td>
<td>-1.29</td>
<td>&lt;0.001</td>
<td>-1.17</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>[-1.95;-0.838]</td>
<td></td>
<td>[-1.86;-0.719]</td>
<td></td>
<td>[-1.86;-0.482]</td>
<td></td>
</tr>
<tr>
<td>NYHA Class</td>
<td>+0.016</td>
<td>&lt;0.001</td>
<td>+0.012</td>
<td>0.009</td>
<td>+0.014</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>[0.007;0.025]</td>
<td></td>
<td>[0.003;0.021]</td>
<td></td>
<td>[0.004;0.024]</td>
<td></td>
</tr>
<tr>
<td>LV Ejection Fraction - %</td>
<td>+0.147</td>
<td>0.142</td>
<td>+0.079</td>
<td>0.445</td>
<td>+0.139</td>
<td>0.268</td>
</tr>
<tr>
<td></td>
<td>[-0.049;0.343]</td>
<td></td>
<td>[-0.124;0.282]</td>
<td></td>
<td>[-0.107;0.386]</td>
<td></td>
</tr>
<tr>
<td>E/e' (medial) Velocity Ratio</td>
<td>+0.130</td>
<td>0.012</td>
<td>+0.067</td>
<td>0.203</td>
<td>+0.027</td>
<td>0.653</td>
</tr>
<tr>
<td></td>
<td>[0.029;0.232]</td>
<td></td>
<td>[-0.036;0.171]</td>
<td></td>
<td>[-0.091;0.145]</td>
<td></td>
</tr>
<tr>
<td>LA Volume Index - mL/m$^2$</td>
<td>+0.313</td>
<td>0.004</td>
<td>+0.232</td>
<td>0.033</td>
<td>+0.148</td>
<td>0.199</td>
</tr>
<tr>
<td></td>
<td>[0.102;0.524]</td>
<td></td>
<td>[0.019;0.444]</td>
<td></td>
<td>[-0.078;0.375]</td>
<td></td>
</tr>
<tr>
<td>LV Mass Index – g/m$^2$</td>
<td>-0.465</td>
<td>0.198</td>
<td>-0.539</td>
<td>0.133</td>
<td>-0.543</td>
<td>0.209</td>
</tr>
<tr>
<td></td>
<td>[-1.17;0.244]</td>
<td></td>
<td>[-1.24;0.164]</td>
<td></td>
<td>[-1.39;0.306]</td>
<td></td>
</tr>
</tbody>
</table>

**Model 1:** Gal-3 only.
**Model 2:** Gal-3 adjusted for Sex, Age.
**Model 3:** Gal-3 adjusted for Sex, Age, Atrial Fibrillation, Blood Pressure (mean arterial pressure), eGFR [mL/min/1.73m$^2$], Hemoglobin [g/dL].
Aldosterone-Receptor Blockade and the Course of Galectin-3 Levels

- No Treatment-effect: P = 0.175
- No Interaction: Galectin-3 * Treatment: P = 0.356
- Spironolactone: P = 0.015
- Placebo: P = 0.091
- Trend (linear): P < 0.001
Galectin-3 at Baseline and Clinical Outcome

Galectin-3

- \( \leq 12.11 \text{ ng/mL} \)
- \( > 12.11 \text{ ng/mL} \)

P=0.259

P=0.263 (adjusted for spironolactone vs. placebo)

Pts. at Risk

<table>
<thead>
<tr>
<th></th>
<th>208</th>
<th>167</th>
<th>196</th>
<th>177</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts. at Risk</td>
<td>207</td>
<td>137</td>
<td>191</td>
<td>170</td>
</tr>
</tbody>
</table>
Course of Galectin-3 and Clinical Outcome

Galectin-3

- no increase during FU
- increase during FU

P=0.015

P=0.016 (adjusted for spironolactone vs. placebo)

Pts. at Risk

<table>
<thead>
<tr>
<th>Time since randomization [months]</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts. at Risk</td>
<td>44</td>
<td>42</td>
<td>42</td>
<td>42</td>
<td>39</td>
</tr>
</tbody>
</table>

Pts. at Risk

<table>
<thead>
<tr>
<th>Time since randomization [months]</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts. at Risk</td>
<td>333</td>
<td>313</td>
<td>287</td>
<td>266</td>
<td>239</td>
</tr>
</tbody>
</table>
Summary

Galectin-3 concentrations are modestly elevated in patients with well-compensated HFpEF, and they are related to different subjective and objective measures of physical performance. In these patients Galectin-3 levels increases over time. This increase predicts subsequent outcome independent of other factors including NT-proBNP.

There is no evidence from this study that spironolactone modulates the observed increase in galectin-3 over time, although spironolactone did improve echocardiographic measures reflective of diastolic filling and ventricular remodeling and did decrease NT-proBNP levels in Aldo-DHF.

Conclusions

These findings especially regarding the prognostic value of galectin-3 provide the foundation for future studies to further evaluate the contribution of galectin-3 to HFpEF pathophysiology and to determine if it is a viable target for therapeutic intervention.
DIAGNOSIS
Exercise test with echocardiography (diastolic stress test)

- Supine bike
- 25 Watts increments
- Assess systolic function
- Mitral inflow (E, A and DT)
- Mitral annulus velocity
- E/e´
- TR velocity
- Recovery

Ha et al. JASE. 2005; 18: 63-8
Alterations in global longitudinal strain (GLS) during the test

GLS increased in controls, but decreased in hypertensive heart disease.

**Controls**

GLS rest: -18,5±3,8
GLS test: -17,6±2,4

**HHD**

GLS rest: -18,0±1,3
GLS test: -22,0±3,8

p > 0,05 vs. rest
Alterations in early diastolic strain rate (e_DSR) during the test

Early diastolic strain rate improved during exercise in controls, but a lesser extent in HHD group.

<table>
<thead>
<tr>
<th></th>
<th>HHD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>e_DSR rest</td>
<td>1,1±0,3</td>
<td>1,0±0,2</td>
</tr>
<tr>
<td>e_DSR test</td>
<td>1,9±0,7*</td>
<td>1,5±0,3*</td>
</tr>
</tbody>
</table>

* p < 0,05 vs. rest
CARDIAC STRUCTURE AND FUNCTION
LA deformation and volumetric function

Kraigher-Krainer E. Et al.

- LAEF
- LA passive EF
- LA active EF
Left Atrial Strain

Normal Control

LA Strain: 46.2 %

HFpEF

LA Strain: 20.1 %
Comparisons made between 1) HFpEF without LAE vs. controls and 2) among HFpEF patients with and without LAE.

* P < 0.001; # p ≤ 0.01; LAE = left atrial enlargement

- P < 0.001; # p ≤ 0.01; LAE = left atrial enlargement;
- Left atrial enlargement defined as LA volume index (to BSA=body surface area) ≥ 29ml/m².

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Kraighe-Krainer E, Solomon SD et al. Presented at HFA 2013
THERAPY
The Effects of Inspiratory Muscle Training in Patients With Heart Failure With Preserved Ejection Fraction

P. Palau Sampio¹, E. Dominguez Mafe², B. Mascarell Gregori¹, E. Nuñez Botero¹, JM. Ramon Ferrandis¹, P. Vergara Lozano³, J. Sanchis Fores¹, FJ. Chorro Gasco¹, J. Nuñez Villota¹

¹Cardiology Department, Hospital Clínic Universitari de Valencia, Valencia, Spain
²Cardiology Department, Hospital General de Castellón, Castellón, Spain
³University of Valencia, Department of Physiotherapy, Valencia, Spain

ClinicalTrials.gov Identifier: NCT01707277
Objective

• A simple and low intensity IMT protocol
• 12-week
• Home-based

Advanced HFpEF and reduced aerobic capacity

Primary endpoint: exercise capacity parameters
• Peak VO2
  • VO2 at anaerobic threshold
  • VE/VCO2 slope
  • METs
  • 6-MWT

Secondary endpoint:
• QoL
• Echo
• Biomarkers (NT-proBNP and CA125)

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Patients with heart failure (NYHA class ≥ 2) and preserved left ventricular ejection fraction, relevant structural heart disease and/or echo signs of diastolic dysfunction and written informed consent.

Randomized n=27

Training group n=14
Control group n=13

Available for analysis n=26
Primary endpoint: changes in exercise capacity parameters

Training group n=14
Control group n=12
Results at 12 weeks

Peak VO2

Change in peak VO2 (mL/min/kg)

Baseline 12 weeks Baseline 12 weeks

p=0.206 p<0.001

Change in METs

Baseline 12 weeks Baseline 12 weeks

p=0.156 p<0.001
Conclusions

- In patients with advanced HFpEF, IMT was associated with marked improvement in exercise capacity and QoL.

- These results provide evidence to suggest that IMT may be considered as a promising therapy in these patients.