ENDOTHELIAL OVEREXPRESSION OF BETA-3 ADRENERGIC RECEPTOR IN RAT, A RELEVANT MODEL OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

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Heart failure with preserved ejection fraction (HFPEF)

- 15 millions heart failure (HF) patients in Europe
- 54% (40-71) have a preserved left ventricular ejection fraction (LVEF)


- HFPEF is an issue for the cardiologist:
  - Complex pathophysiology
  - No efficient treatment to improve HFPEF-related morbi-mortality

Basic science in HFPEF

• Difficulty to find animal models close to human HFPEF:
  – Existing models are associated with high levels of afterload: hypertension, aortic banding
  – Early alteration of the ejection fraction
A new original model?

- Transgenic rat overexpressing the $\beta_3$-adrenergic receptor in the endothelium (Tg$\beta_3$)

- **Aims of the study:**
  - To characterize the hemodynamic phenotype of 12 weeks-old Tg$\beta_3$ rats
  - To compare this phenotype with human HFPEF pathophysiology
The endothelial $\beta_3$-adrenergic receptor ($\beta_3$-AR)

Rozec and Gauthier, Pharmacol & Therap, 2006, 111, 652-657.
Animal model: rat overexpressing human $\beta_3$-AR in the endothelium

- Human cDNA of $\beta_3$-AR + gene promoter ICAM-2

$\Rightarrow$ Exclusive endothelial location

$\Rightarrow$ Human $\beta_3$-AR is exclusively located in cardiac endothelial cells in TG$\beta_3$ heart
The hemodynamic phenotype of Tgβ₃

Heart rate (bpm)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>359</td>
<td>±15</td>
</tr>
<tr>
<td>Tgβ₃</td>
<td>364</td>
<td>±13</td>
</tr>
</tbody>
</table>

Mean arterial pressure (mm Hg)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>95</td>
<td>±6</td>
</tr>
</tbody>
</table>
| Tgβ₃     | 115  | ±4  *

LV ejection fraction

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>82 ± 2 %</td>
</tr>
<tr>
<td>Tgβ₃</td>
<td>79 ± 2 %</td>
</tr>
</tbody>
</table>

LV end-diastolic pressure (mm Hg)

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>6.5 ± 1.2</td>
</tr>
<tr>
<td>Tgβ₃</td>
<td>12.7 ± 1.4 *</td>
</tr>
</tbody>
</table>
Systolic myocardial deformations

Altered radial strain in Tgβ₃

Wild Type (n = 16): 40 ± 4.97%

Tgβ₃ (n = 11): 24 ± 2.83%, p < 0.05 vs WT

Control

HFPEF

Diastolic function

LV relaxation parameters

<table>
<thead>
<tr>
<th></th>
<th>WT</th>
<th>Tgβ3</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>E wave (cm/s)</td>
<td>95.4 ± 3.7</td>
<td>86.7 ± 5.0</td>
<td>NS</td>
</tr>
<tr>
<td>E’ wave (cm/s)</td>
<td>4.73 ± 0.43</td>
<td>4.78 ± 0.42</td>
<td>NS</td>
</tr>
<tr>
<td>Min DP/dt (mm Hg/s)</td>
<td>-6781 ± 475</td>
<td>-8075 ± 722</td>
<td>NS</td>
</tr>
<tr>
<td>Tau (ms)</td>
<td>8.37 ± 0.40</td>
<td>8.17 ± 0.25</td>
<td>NS</td>
</tr>
</tbody>
</table>

LV stiffness constant, β

- WT: 1.34
- Tgβ3: 2.12

- WT: 6
- Tgβ3: 7

NS: Not Significant
Ventriculo-arterial interaction

Arterial Elastance (Ea, mm Hg/ml)

WT: 246 ± 32
Tgβ3: 329 ± 35 *

LV End-systolic elastance
(Ees, end-systolic pressure at midrange LV volume)

WT: 32.7 ± 3.4
Tgβ3: 57.2 ± 3.6 *

* p < 0.05 vs WT

Increased ventricular-arterial stiffness
Ventriculo-arterial interaction

Ventriculo-arterial stiffening in Tgβ3

Human HFPEF

Conclusions

• $\text{Tg}\beta_3$ presents a hemodynamic phenotype close to human HFPEF pathophysiology:
  
  – Increased ventricular-arterial stiffness
  – Increased LV diastolic stiffness
  – Altered LV systolic myocardial deformations

• An original model:
  
  – Transgenic
  – Lower afterload levels than other animal models
  – Implication of the endothelium in HFPEF pathophysiology
Perspectives

• To study the effects of conditions associated with acute HF in HFPEF patients:
  – Effects of ageing
  – Volume overload
  – Tachycardia or chronotropic incompetence

• To study potential cellular mechanisms implicated in HFPEF pathophysiology:
  – The endothelial β₃-AR and its signaling pathway (NO, phosphodiesterases)
  – To test pharmacological substances on those molecular targets
Acknowledgements

G. TOUMANIANTZ  I. ANEGON  S. MENORET
S. ERBIBOU  M. ERFANIAN
T. TRAN-QUANG
N. MERLET  C. SEZE-GOISMIER
L. AUDIGANE
Endothelial overexpression of $\beta_3$-AR induces a remodeling of $\beta_1$- and $\beta_2$-AR in cardiomyocytes

![Bar chart showing mRNA expression ratio (RT-PCR) for $\beta_1$-AR and $\beta_2$-AR in WT and Tg$\beta_3$.](chart1.png)

![Graph showing peak tension of papillary muscle in response to log [Isoproterenol] M for WT and Tg$\beta_3$.](chart2.png)
Endothelial overexpression of the $\beta_3$-AR is associated with a specific negative inotropic effect of $\beta_3$-AR stimulation involving the NO pathway on papillary muscles.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>WT (n = 11)</th>
<th>TG β₃ (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (mm)</td>
<td>8.07 ± 0.25</td>
<td>8.19 ± 0.23</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>4.30 ± 0.25</td>
<td>4.69 ± 0.30</td>
</tr>
<tr>
<td>SIVd (mm)</td>
<td>1.73 ± 0.09</td>
<td>1.71 ± 0.06</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>1.49 ± 0.06</td>
<td>1.43 ± 0.06</td>
</tr>
<tr>
<td>Fraction shortening (%)</td>
<td>47.0 ± 2.3</td>
<td>43.5 ± 2.2</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>82.3 ± 2.1</td>
<td>78.7 ± 2.3</td>
</tr>
<tr>
<td>E wave peak (cm.s⁻¹)</td>
<td>95.4 ± 3.7</td>
<td>86.7 ± 5.0</td>
</tr>
<tr>
<td>E' (cm.s⁻¹)</td>
<td>4.73 ± 0.43</td>
<td>4.78 ± 0.32</td>
</tr>
<tr>
<td>E/E'</td>
<td>21.8 ± 2.1</td>
<td>20.9 ± 0.01</td>
</tr>
<tr>
<td>Mitral Sa wave (cm.s⁻¹)</td>
<td>5.27 ± 0.59</td>
<td>6.11 ± 0.89</td>
</tr>
<tr>
<td>Global circumferential strain (%)</td>
<td>- 16.39 ± 0.97</td>
<td>- 11.34 ± 0.66 *</td>
</tr>
<tr>
<td>Mean of peak radial strain (%)</td>
<td>40.56 ± 4.97</td>
<td>23.67 ± 2.83 *</td>
</tr>
</tbody>
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