Exercise PVR: A Key Predictor of Benefit of Atrial Shunt Therapy in HFpEF?

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## Pre-specified subgroup analyses

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>IRR (95% CI)</th>
<th>(P_{\text{interaction}})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>239</td>
<td>1.32 (1.01-1.71)</td>
<td>0.020</td>
</tr>
<tr>
<td>Female</td>
<td>382</td>
<td>0.85 (0.55-1.09)</td>
<td></td>
</tr>
<tr>
<td><strong>RA volume index</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertile 1</td>
<td>167</td>
<td>0.79 (0.57-1.11)</td>
<td>0.012</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>168</td>
<td>0.70 (0.46-1.07)</td>
<td></td>
</tr>
<tr>
<td>Tertile 3</td>
<td>168</td>
<td>1.43 (1.08-1.90)</td>
<td></td>
</tr>
<tr>
<td><strong>PA systolic pressure at 20W</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertile 1</td>
<td>192</td>
<td>0.71 (0.46-1.11)</td>
<td></td>
</tr>
<tr>
<td>Tertile 2</td>
<td>202</td>
<td>0.80 (0.57-1.12)</td>
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<tr>
<td>Tertile 3</td>
<td>202</td>
<td>1.40 (1.10-1.79)</td>
<td></td>
</tr>
</tbody>
</table>

Statistical significance threshold: interaction p-value < 0.05
Responder analysis

**PA pressure** = \( PVR \times CO + PCWP \)

- **Markers of pulmonary vascular disease**
  - PVR at rest, peak
  - PASP at rest, legs up, 20W, peak
  - TPR (mPAP/CO) at rest, peak
  - PA compliance at rest/peak
  - PASP/SV at rest, peak

- **Hemodynamic markers of RV dysfunction**
  - PCWP-CVP at rest, legs up, 20W, peak
  - TAPSE/PASP ratio

- **Time to first HF event**
- **Total (first and recurrent) HF events**
- **Change in KCCQ, baseline to 12 months**
What is a normal peak exercise PVR?

- Study of 55 healthy participants
- Right heart catheterization
- Mean age 50, 36% age >55
- Similar resting hemodynamics in both age groups (<55 and >55 yrs)
- Older healthy individuals have ↑PA pressure and ↑PCWP, ↓CI during exercise
- Mean peak PVR = 1.0, SD = 0.4 WU
- **Peak exercise PVR upper limit of normal (mean+2SD): 1.8 WU**

Latent PVD: worse outcomes with IASD

Latent PVD = peak exercise PVR ≥1.74 WU (highest tertile)
Resting vs. exercise PVR in REDUCE II

A

\[ PVR_{EX} = 0.68 \times PVR_{REST} + 0.39 \]

\[ R^2 = 0.38 \]

B

Exercise Change in PVR (WU)

Resting PVR (WU)

No Latent PVD

Latent PVD
Peak exercise PVR vs. delta PCWP, RAP

### PCWP

- **Equation:** $R = -0.20$, $P < 0.0001$
- Scatter plot showing a negative correlation between peak exercise PVR (WU) and pressure difference, rest to peak exercise (mmHg).

### RA Pressure

- **Equation:** $R = +0.20$, $P < 0.0001$
- Scatter plot showing a positive correlation between peak exercise PVR (WU) and pressure difference, rest to peak exercise (mmHg).
Effect of shunt on KCCQ by peak exercise PVR

Sham control
Atrial shunt device

Change in KCCQ- OSS, baseline to 12 months

Peak exercise PVR (WU)
Effect of shunt on KCCQ by ± latent PVD

Change in KCCQ OSS at 12 months, No PVD

- Shunt: p=0.010
- Sham

Change in KCCQ at 12 months, Latent PVD

- Shunt: p=0.008
- Sham

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Effect of shunt on echo by ± latent PVD

No latent PVD (peak exercise PVR <1.74 WU)

<table>
<thead>
<tr>
<th>Echo change variable (baseline to 12 months)</th>
<th>Shunt device</th>
<th>Sham control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA volume</td>
<td>↑</td>
<td>↔</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV end-diastolic volume</td>
<td>↑</td>
<td>↔</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TAPSE</td>
<td>↔</td>
<td>↔</td>
<td>0.25</td>
</tr>
<tr>
<td>TR severity</td>
<td>↑</td>
<td>↔</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LA volume</td>
<td>↔</td>
<td>↔</td>
<td>0.90</td>
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<tr>
<td>LV end-diastolic volume</td>
<td>↔</td>
<td>↔</td>
<td>0.16</td>
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<tr>
<td>LVEF</td>
<td>↔</td>
<td>↔</td>
<td>0.97</td>
</tr>
</tbody>
</table>

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Effect of shunt on echo by ± latent PVD

**Latent PVD (peak exercise PVR ≥1.74 WU)**

<table>
<thead>
<tr>
<th>Echo change variable (baseline to 12 months)</th>
<th>Shunt device</th>
<th>Sham control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA volume</td>
<td>↑</td>
<td>↑</td>
<td>0.227</td>
</tr>
<tr>
<td>RV end-diastolic volume</td>
<td>↑</td>
<td>↑</td>
<td>0.367</td>
</tr>
<tr>
<td>TAPSE</td>
<td>↔</td>
<td>↔</td>
<td>0.366</td>
</tr>
<tr>
<td>TR severity</td>
<td>↑</td>
<td>↑</td>
<td>0.956</td>
</tr>
<tr>
<td>LA volume</td>
<td>↔</td>
<td>↔</td>
<td>0.383</td>
</tr>
<tr>
<td>LV end-diastolic volume</td>
<td>↓</td>
<td>↔</td>
<td>0.008</td>
</tr>
<tr>
<td>LVEF</td>
<td>↔</td>
<td>↔</td>
<td>0.481</td>
</tr>
</tbody>
</table>

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Responder analysis

Latent PVD = peak exercise PVR ≥1.74 WU

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Overall efficacy of shunt by peak exercise PVR

• ~50% of patients had exercise PVR <1.74 and no pacemaker
• These patients had more “wins” when treated with atrial shunt device (↓HF hospitalizations and ↑health status)
• Opposite was true in those with exercise PVR ≥1.74 or pacemaker
Future directions: ↑Precision medicine

ALL suspected HFpEF

Definite HFpEF
(exercise PCWP ≥25 mmHg)

Excluding RV
dysfunction, ≥2+ TR,
resting PVR >3.5 WU

Excluding PVD
during exercise
and PM

Most major pharma trials

REDUCE LAP-HF II trial

Large potential responder
group for future trials of
interatrial shunt devices
(~50% of patients enrolled)

*PVD = pulmonary vascular disease,
defined as abnormal
↑PVR during exercise
(~1.8 WU or higher)
PM = pacemaker