Right Ventricular Stroke Work Correlates With Outcomes in Pediatric Pulmonary Arterial Hypertension (PAH) Patients

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Pulmonary arterial hypertension (PAH): PAP $>25$ mmHg and PVR $>3$ WU

- Progression is highly variable and poorly understood (5-year survival rates: 60-70%).
- Endpoints are not well characterized in children (e.g. 6MW).
- Need improved clinical markers

Van Loon et al., Circulation, 2011
Pressure-volume (P-V) loops characterize ventricular performance.

Right ventricular stroke work (RVSW): area enclosed by the P-V loop.
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P-V loops are difficult to measure routinely.
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Right ventricular stroke work (RVSW): area enclosed by the P-V loop

P-V loops are difficult to measure routinely.

Goals: assess RVSW in pediatric patients with PAH:

\[ RVSW = \int_0^T P(t)V(t)dt, \quad RVSW_{BSA} = \frac{RVSW}{BSA^{1.407}} \]

\[ RVSW_{EF} = \frac{RVSW_{BSA}}{EF} \]
Methods

- Use computational modeling + routinely measured clinical data
  - Lumped parameter model (LPM): use electric circuits to model hemodynamics
  - Right heart catheterization (RHC): RV and PA pressures
  - MRI: RV volumes (EDV and ESV) and PA flow
- Tune LPM to match RHC/MRI measurements by optimization.
### Study Design

<table>
<thead>
<tr>
<th></th>
<th>Stable n=9</th>
<th>Worsening* n=8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>n=4</td>
<td>n=4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>10.7(4.9-16.3)</td>
<td>8.4(4.4-13.5)</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.0(0.6-1.7)</td>
<td>0.9(0.7-1.8)</td>
</tr>
<tr>
<td>IPAH</td>
<td>n=5</td>
<td>n=7</td>
</tr>
<tr>
<td>Prostacyclin therapy</td>
<td>n=3</td>
<td>n=7</td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>4.2(1.2-8)</td>
<td>3.7(1.1-6)</td>
</tr>
<tr>
<td>PVRI (WU × m²)</td>
<td>6.8 (5.2-31.6)</td>
<td>14.8 (8.1-24.7)</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>48(30-55)</td>
<td>48(18-54)</td>
</tr>
</tbody>
</table>

- **Inclusion criteria**
  - Age<18
  - IPAH or PAH-CHD
  - multiple paired RHC/MRI (n≥2)

- **17 patients with 61 data points**
- *Clinical worsening: death, listed or considered for transplantation, poor hemodynamic responses to maximal therapy*
Results

a) Stable

b) Worsening

- Patients with clinical worsening have increased RVSW.
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Quantities of interest are grouped and compared by outcomes (stable vs clinical worsening) within 2 years following RHC/MRI.
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- Quantities of interest are grouped and compared by outcomes (stable vs clinical worsening) within 2 years following RHC/MRI.
- A linear mixed model is used to test the associations between predictors and outcomes.
Results

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(a) $RV_{SWF}$

- Stable
- Worsening

$P < 0.0001$

$n = 55$
$n = 6$

1 yr following MRI/RHC

(b) $RV_{SWF}$

- Stable
- Worsening

$P = 0.0007$

$n = 47$
$n = 13$

2 yrs following MRI/RHC

(c) $RV_{SWF}$

- Stable
- Worsening

$P = 0.0002$

$n = 25$
$n = 25$

5 yrs following MRI/RHC

(d) $PVRI$

- Stable
- Worsening

$P = 0.11$

$n = 55$
$n = 6$

1 yr following MRI/RHC

(e) $PVRI$

- Stable
- Worsening

$P = 0.17$

$n = 47$
$n = 13$

2 yrs following MRI/RHC

(f) $PVRI$

- Stable
- Worsening

$P = 0.04$

$n = 25$
$n = 25$

5 yrs following MRI/RHC

(g) $R_P : R_S$

- Stable
- Worsening

$P = 0.02$

$n = 55$
$n = 6$

1 yr following MRI/RHC

(h) $R_P : R_S$

- Stable
- Worsening

$P = 0.002$

$n = 47$
$n = 13$

2 yrs following MRI/RHC

(i) $R_P : R_S$

- Stable
- Worsening

$P = 0.002$

$n = 25$
$n = 25$

5 yrs following MRI/RHC
\[ y = 319.01x + 2457.5 \]

\[ R^2 = 0.3775 \]

\[ p < 1 \times 10^{-6} \]
RV SWEF is an independent predictor.
Receiver operating characteristic (ROC)

- TPR: true positive rate = sensitivity, FPR: false positive rate = 1 - specificity
- RVSW outperforms PVRI and Rp:Rs for predicting worsening 2 years following RHC/MRI (AUC: 0.86 vs 0.74 vs 0.79).
- Cutoff values for 90% spec. RVSW = 8593, PVRI = 19, Rp:Rs = 1.1
## Receiver operating characteristic (ROC)

### 1 year following MRI/RHC

<table>
<thead>
<tr>
<th>RV SW&lt;sub&gt;EF&lt;/sub&gt;</th>
<th>PVRI</th>
<th>Rp:Rs</th>
<th>EF</th>
<th>EDVI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC</strong></td>
<td>0.93</td>
<td>0.78</td>
<td>0.83</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Cutoff values</strong></td>
<td>10027</td>
<td>22</td>
<td>1.29</td>
<td>37%</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>0.67</td>
<td>0.2</td>
<td>0.17</td>
<td>0.67</td>
</tr>
</tbody>
</table>

### 2 years following MRI/RHC

<table>
<thead>
<tr>
<th>RV SW&lt;sub&gt;EF&lt;/sub&gt;</th>
<th>PVRI</th>
<th>Rp:Rs</th>
<th>EF</th>
<th>EDVI</th>
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<tr>
<td><strong>AUC</strong></td>
<td>0.86</td>
<td>0.74</td>
<td>0.79</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>Cutoff values</strong></td>
<td>8593</td>
<td>19</td>
<td>1.1</td>
<td>37%</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>0.62</td>
<td>0.39</td>
<td>0.38</td>
<td>0.38</td>
</tr>
</tbody>
</table>

### 5 years following MRI/RHC

<table>
<thead>
<tr>
<th>RV SW&lt;sub&gt;EF&lt;/sub&gt;</th>
<th>PVRI</th>
<th>Rp:Rs</th>
<th>EF</th>
<th>EDVI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC</strong></td>
<td>0.85</td>
<td>0.78</td>
<td>0.83</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>Cutoff values</strong></td>
<td>8160</td>
<td>19</td>
<td>1.1</td>
<td>34%</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>0.6</td>
<td>0.32</td>
<td>0.36</td>
<td>0.24</td>
</tr>
</tbody>
</table>
RV stroke work in children with pulmonary arterial hypertension: estimation based on invasive haemodynamic assessment and correlation with outcomes

Michael V Di Maria,1 Adel K Younoszai,1 Luc Mertens,2 Bruce F LandeckII,1
D Dunbar Ivy,1 Kendall S Hunter,3 Mark K Friedberg2

RVSW=mPAPxSV
Cath derived mPAP
Echo derived SV

- RVSW is associated with WHO classification.
- RVSW is reduced in class IV.
- RVSW was not found be superior to PVRI.
- RVSW by mPAPxSV might underestimate RVSW by up to 35%.

Figure 1  Indexed RV stroke work (RVSW) by WHO class. When grouped by WHO heart failure class, there was a significant difference in indexed RVSW (p=0.04). RVSW appeared to trend upward in WHO classes 1, 2, and 3, but showed a decline in WHO class 4. Box plots presented here feature the median as a horizontal line within the box, while the box itself represents the IQR (25–75th); the ‘whiskers’ represent the bounds of the extreme values in which Q3+1.5(Q3-Q1) and Q1–1.5*(Q3-Q1), respectively, and single points are, therefore, outliers.

Di Maria et al., Heart, 2014
▶ Patient specific RVSW and P-V loops can be modeled easily.
▶ RVSW correlates with symptomatic/disease worsening in pediatric PAH.
▶ RVSW outperforms PVRI and Rp:Rs for predicting clinical worsening in pediatric patients with PAH.
▶ Future studies will include validation and a larger cohort of patients.
▶ Translate computational modeling into clinical practice: a website/mobile app based risk calculator for PAH patients.