Pathophysiology of PH: the right heart matters

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Severe PH: a disease of progressive RV-arterial uncoupling, with RV function determining symptomatology and outcome.

A. Pathobiologic/pathologic progression, increased PVR

B. Heart chambers response, RV failure

1. RV function in PAH determines maximum cardiac output, aerobic exercise capacity – and survival
Q and VO$_2$ are linearly correlated to work output during exercise.

Guyton, Texbook of Medical Physiology
Naeije R, Chest 2010; 137: 1259-60
Q and VO$_2$ are linearly correlated to work output or distance/time during exercise.

Running speed (6MWD)

Guyton, Texbook of Medical Physiology
Naeije R, Chest 2010; 137: 1259-60
6-MWD, peak VO$_2$, NYHA, resting PAP and cardiac output, and survival in IPAH

6MWD predicted survival
6MWD was correlated to peak VO$_2$, NYHA, and resting cardiac output, not to PAP

Only 6MWD was an independent predictor of survival and clinical stability of all PAH (IPAH or APAH), whether prevalent or incident. VE/VCO2 predicted survival only in IPAH, (peak VO2 borderline).
The notion that targeted therapies would shift PAH patients to better functional state and survival curves.
Meta-analysis of RCT of prostacyclins, ERA’s and PDE5i’s in PAH

Galié et al, Eur Heart J 2009; 30: 394–403
Macchia et al, Am Heart J 2010; 159: 245-257

<table>
<thead>
<tr>
<th></th>
<th>Galié, 2009</th>
<th>Macchia, 2010</th>
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</thead>
<tbody>
<tr>
<td>Trials, n</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>PAH pts, n</td>
<td>3140</td>
<td>3519</td>
</tr>
<tr>
<td>6MWD, m</td>
<td>+ 36</td>
<td>+ 38</td>
</tr>
<tr>
<td>PAP, mmHg*</td>
<td>- 2.9</td>
<td>- 3.9</td>
</tr>
<tr>
<td>PVR, wu*</td>
<td>- 4.1</td>
<td>- 3.5</td>
</tr>
<tr>
<td>Mortality</td>
<td>- 43 %</td>
<td>- 39 %</td>
</tr>
</tbody>
</table>

* Respectively 11 and 12 trials
Do changes in the 6MWD predict clinical events in patients with PAH? Savarese et al, JACC 2012; 60: 1192-1201

- 32 RCT’s enrolling 3112 patients

- Active treatments led to significant reductions of mortality and clinical events (> 24 h hospitalisation for PAH, rescue therapies, transplantations and death)

- Δ 6MWD was correlated to Δ PVR, but there was no relationship between Δ6MWD and outcome
Meta-Regression Analysis Meta-regression between (A) Δ6MWD and composite outcome, (B) all-cause death, (C) hospitalization for pulmonary arterial hypertension (PAH) and/or lung or heart-lung transplantation, (D) and initiation of PAH rescue therapy.
What is the explanation for this paradox?

Answer: $\Delta s$ are approximately $1/10$ of absolute values while SDs remain the same, thus causing an excessive decrease in signal to noise ratio.

Example: A drug increases the 6MWD from $400 \pm 40$ m to $440 \pm 40$ m, $P < 0.001$ while the 6MWD remains at $410 \pm 40$ m in controls, - F value of analysis of variance $P < 0.01$

But on $\Delta s$: $40 \pm 40$ compared to $10 \pm 40$ m, $P$ is NS
16 RCT’s enrolling 2353 patients, follow-up 16 ±11 wk

Active treatments led to significant reductions of mortality and clinical events (> 24 h hospitalisation for PAH, rescue therapies, transplantations and death)

There was no relationship between Δ’s of PAP, CI, PVR or RAP and outcome
There is no reason for bashing the 6-min walk test, cardiac output, or right atrial pressure, or PVR, in patients with PAH.

The 6-min walk distance reflects the capability of the RV to increase flow output in response to peripheral demand.

_Naeije R, Chest 2010; 137(6):1258-60._
2. How the RV fails in PAH and how to measure it more specifically
RV failure in PAH: from homeometric to heterometric adaptation

Male
Age 25 yr, NYHA II
mPAP = 56 mmHg

Female
Age 24 yr, NYHA III
mPAP = 53 mmHg

Stroke volume = 90 ml, 6MWD 550 m

Stroke volume = 30 ml, 6MWD 300 m

A Vonk Noordegraaf
Definition of (Right) Heart Failure in Pulmonary Hypertension

Right heart failure is a dyspnea fatigue syndrome with eventual systemic congestion caused by the insufficient adaptation of systolic function (homeometric adaptation, Anrep) to increased afterload and involvement of increased dimensions (heterometric adaptation, Starling) to maintain RV flow output adapted to metabolic demand.

After Sagawa et al. Cardiac contraction and the PV relationship, Oxford University Press, 1988, Endorsed by RV summit (Boston, October 2012) and PH World Symposium (Nice, February 2013)
Vonk Noordegraaf et al, JACC 2013;62:D22–33
Naeije et al, Pulm Circ 2014; 4: 395-406
### Parameters of RV function

#### Echocardiography
- Right atrial area\(^1\)
- RV area\(^1\)
- TAPSE\(^1,2,3\)
- Tei index\(^4\)
- Right ventricular fractional area change\(^3\)
- Degree of tricuspid regurgitation\(^3\)
- Pericardial effusion\(^5,6\)
- Inferior vena cava collapsibility\(^7\)
- Left ventricular eccentricity index\(^3,6\)
- 3D RV strain, EF and asynchrony\(^8\)
- RV IVV\(^9\)
- RV dP/dt\(^10\)

#### MRI
- RV ejection fraction\(^11,12\)
- RV stroke volume\(^11\)
- RV mass\(^11\)
- RV volume\(^11\)

#### RHC
- Right arterial pressure\(^13,14\)
- Cardiac index\(^14\)

#### Biomarkers
- N-terminal pro-brain natriuretic peptide\(^15\)
- Troponin T\(^16\)

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TAPSE: tricuspid annular plane systolic excursion
142 pts with severe PAH (n=105) or CTEPH (n=37)
Univariate analysis: 6MWD, NYHA, EI, RA area, S, TAPSE, IVRT, εL , IVV
Multivariate analysis: 6MWD (P<0.05) and IVV (P<0.005)

RV isovolumic contraction velocity predicts survival in PH
Ernande, Huez, Naeije, Derumeaux et al, JASE 2013;26:297-306
3D speckle tracking of the RV
Smith BCF et al, JACC 2014; 64: 41-51

- 3D-ST > 2D-ST because it is not slice-plane limited and delivers vectorial data in 3 orthogonal planes
- 3D ST allows for optimal measurement of dyssynchrony
- 3D echo allows for RV volume measurements

- 97 patients with PH
- Area strain, circumferential strain and indices of systolic dyssynchrony (SD of mean time to peak systolic strain for 7 RV segments) strongly correlated with RVEF

- Only area strain independently predicted survival
Measurements of dyssynchrony (strain/time), correlations with RVEF, and prediction of survival

Only AS was an independent predictor of survival

Smith et al, JACC 2014; 64: 41-51
RVEF as predictor of survival in patients with PAH Van de Veerdonk et al, JACC 2011;58:2511-9

- 110 patients with incident PAH
- Baseline RVEF (hazard ratio [HR]: 0.938; p = 0.001) and PVR (HR: 1.001; p = 0.031) were predictors of mortality
- Changes in RVEF were associated with survival
RV function to predict survival in patients referred for PH Vanderpool, Naeije et al, Heart 2015; 101: 37-43

- 50 patients referred for severe severe PH
- Higher RAP, mPAP, PVR and $\beta$, and lower SV, EF and Ees/Ea all predicted outcome at univariate analysis – at multivariable analysis, \( \text{SV/ESV} \) (not SV/EDV) was the only independent predictor
3. The emerging importance of RV contractile reserve

N=124, stress echo, contractile reserve defined by exercise-induced increase in SPAP.
4. What is the therapeutic relevance of improved measurements of RV function?
Investigation of the mechanisms of right heart failure Voelkel et al, Pulm Circ 2013;3:137-143

The RV between a rock and a hard place
Improved in RV-arterial coupling with bisoprolol in rats with monocrotaline-induced PH

De Man et al, Circ Heart Fail 2012;5:97-105
Improved survival with low dose bisoprolol

Hazard ratio PH+Beta vs. PH-Beta = 0.2 (95% CI 0.1 - 0.9)

$p=0.03$

De Man et al, Circ Heart Fail 2012;5:97-105

- Upfront triple combo Rx i.v. epoprostenol + bosentan + sildenafil
- 18 newly diagnosed (i.e. incident) Idiopathic (11) /Heritable (7) PAH patients
- Mean age 40 ± 14 years (17 – 63)
- NYHA III (7) or IV (11) / 6MWD = 228 ± 164 m (0 – 415)

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP, mmHg</td>
<td>13 ± 4</td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>69 ± 16</td>
</tr>
<tr>
<td>wPAP, mmHg</td>
<td>9 ± 3</td>
</tr>
<tr>
<td>CI, L.min⁻¹.m⁻²</td>
<td>1.7 ± 0.3</td>
</tr>
<tr>
<td>PVR, dyn.s.cm⁻⁵</td>
<td>1716 ± 605</td>
</tr>
<tr>
<td>SvO₂, %</td>
<td>48 ± 10</td>
</tr>
</tbody>
</table>
**Up-front triple combo Rx: first follow-up**

- Two patients died before starting any treatment
- One patient failed and underwent urgent HLT (D118) before reassessment
- Dramatic improvement in the remaining 15 patients

<table>
<thead>
<tr>
<th>N = 15</th>
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</thead>
<tbody>
<tr>
<td>NYHA FC I : II : III : IV, n</td>
<td>Baseline</td>
<td>First f-up (4 ± 1 mo.)</td>
<td>P-value</td>
<td></td>
</tr>
<tr>
<td>0 : 0 : 7 : 8</td>
<td>1 : 13 : 1 : 0</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-min walk distance, m</td>
<td>248 ± 168</td>
<td>451 ± 83</td>
<td>&lt;.0003</td>
<td></td>
</tr>
<tr>
<td>Haemodynamics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA pressure, mmHg</td>
<td>13 ± 5</td>
<td>5 ± 5</td>
<td>&lt;.0002</td>
<td></td>
</tr>
<tr>
<td>Mean PAP, mmHg</td>
<td>67 ± 14</td>
<td>46 ± 14</td>
<td>&lt;.0005</td>
<td></td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>1.7 ± 0.3</td>
<td>3.6 ± 0.7</td>
<td>&lt;.00001</td>
<td></td>
</tr>
<tr>
<td>PVR, dyn.s.cm⁻⁵</td>
<td>1604 ± 469</td>
<td>537 ± 228</td>
<td>&lt;.00001</td>
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<tr>
<td>Mean BP, mmHg</td>
<td>92 ± 13</td>
<td>81 ± 12</td>
<td>&lt;.002</td>
<td></td>
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<tr>
<td>Heart rate, bpm</td>
<td>92 ± 11</td>
<td>85 ± 10</td>
<td>.052</td>
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<tr>
<td>SvO₂, %</td>
<td>50 ± 9</td>
<td>70 ± 5</td>
<td>&lt;.00007</td>
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<tr>
<td>Epoprostenol dose, ng/kg/min</td>
<td>0</td>
<td>16 ± 2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Courtesy O Sitbon
Up-front triple combo Rx: last follow-up

- Mean follow-up = 24 ± 12 months (range: 6 - 52 mo.)
- All 15 patients alive, in NYHA class I-II
- 12 patients reassessed after 9 - 51 months

<table>
<thead>
<tr>
<th>N = 12</th>
<th>Baseline</th>
<th>First f-up (4 ± 1 mo.)</th>
<th>Last f-up (23 ± 12 mo.)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>NYHA FC I : II : III : IV, n</td>
<td>0 : 0 : 5 : 7</td>
<td>0 : 12 : 0 : 0</td>
<td>2 : 10 : 0 : 0</td>
<td>&lt;.001</td>
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<tr>
<td>6-min walk distance, m</td>
<td>242 ± 160</td>
<td>449 ± 52</td>
<td>490 ± 39</td>
<td>&lt;.01</td>
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<tr>
<td>Haemodynamics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA pressure, mmHg</td>
<td>13 ± 5</td>
<td>5 ± 5</td>
<td>6 ± 5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean PAP, mmHg</td>
<td>65 ± 15</td>
<td>46 ± 14</td>
<td>43 ± 12</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>1.7 ± 0.3</td>
<td>3.6 ± 0.6</td>
<td>3.7 ± 0.7</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>PVR, dyn.s.cm⁻⁵</td>
<td>1603 ± 505</td>
<td>534 ± 206</td>
<td>475 ± 233</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Mean BP, mmHg</td>
<td>92 ± 14</td>
<td>80 ± 10</td>
<td>85 ± 20</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>95 ± 11</td>
<td>85 ± 11</td>
<td>81 ± 13</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>SvO₂, %</td>
<td>51 ± 9</td>
<td>70 ± 4</td>
<td>72 ± 6</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Epoprostenol dose, ng/kg/min</td>
<td>0</td>
<td>16 ± 1</td>
<td>18 ± 4</td>
<td></td>
</tr>
</tbody>
</table>

Courtesy O Sitbon
Conclusions

1. The WSPH 2013 in Nice underscored that P(A)H is a RVF syndrome

2. Measurements of RV function best include volumes and indices of systolic function and dyssynchrony – optimal method likely to become 3D echo – or MRI

3. Better measurements of the RV will likely improve current therapeutic approaches to patients with PAH