Διαγνωστικές και Θεραπευτικές Προκλήσεις στην Πνευμονική Υπέρταση με βάση τα τελευταία δεδομένα:

Ο ρόλος της δεξιάς κοιλίας στην Πνευμονική Αρτηριακή Υπέρταση

Σοφία Αναστασία Μουράτογλου
Ειδ/νη Καρδιολογίας
None
Leonardo da Vinci showed that
blood flowed from the right ventricle to the lungs, and from there to
the pulmonary vein 'to mix with air.' There may have been a
premonition of the idea of capillaries in this observation
right ventricle drew blood that originated in the liver, as taught by
Galen, and conveyed it to the lungs.

1450 - the discovery of the “Right heart”

“The right ventricle may be said to be made for the
sake of transmitting blood through the lungs, not
for nourishing them.”

William Harvey, Exercitatio
Anatomica de Motu Cordis et
Sanguinis in Animalibus, 1628
The peculiar characteristics of the right heart

• **Anatomy** (thinned wall RV, triangular shape) cannot guarantee a forward flow at a low cost
• **Adaptation** to pressure load is impressive in chronic conditions and disappointing in acute ones
• **Function** depends on either heterometric and homeometric mechanism similar to LV.
• **Contraction** is primarily dependent on IV septum.
RV reserve in exercise

Lewis GD et al, Circulation 2013
Let the RV help tell the story…

- Unlike the LV, the RV is thin walled and distensible

The RV is afterload-sensitive

Redington A et al, Br Heart J 1988
The Right Ventricle and Its Load in Pulmonary Hypertension

Pulmonary vessel narrowing leads to increased vascular load on right ventricle (RV)

RV adapts by increasing muscle contractility and wall thickness ("coupling")

To maintain cardiac output, RV dilates and heart rate increases
Increase in wall stress and oxygen consumption per gram follow
Leftward septal bowing results

Final stage: Uncoupling occurs with high metabolic demand and reduced output
RV abrupt hemodynamic decompensation

Guyton AC. Circ Res. 1954
Greyson CR. Crit Care Med. 2008
Does RV works alone?

It takes two to tango...
A coupling is a device used to connect two shafts together at their ends for the purpose of transmitting power. Couplings do not normally allow disconnection of shafts during operation.

But, what is “coupling”?

Vonk Noordegraaf et al, JACC 2017

Right-sided heart failure is characterized by low cardiac output and/or elevated right-sided filling pressures due to systolic and/or diastolic right ventricular dysfunction.

Right-sided heart failure is severe if it leads to secondary dysfunction of other organs and tissues, in particular liver, kidneys and gut.
The effect of PH on the LV...

(A) \( \downarrow \) Coronary perfusion pressure + \( \uparrow \) \( O_2 \) Demand = \( \downarrow \) Supply/Demand

(B) \( \uparrow\uparrow \) RV Distention \& \( \uparrow \) LV Filling = \( \downarrow \) Cardiac Output
Curvature duration index

Additive value of CDi (≥67%) for known survival predictors in pulmonary arterial hypertension calculated using multivariable Cox regression analysis modeling

<table>
<thead>
<tr>
<th>Model</th>
<th>Multivariable analysis</th>
<th>Model comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>-2 LL</td>
</tr>
<tr>
<td>Model A (6MWD≤413m)</td>
<td>3.77</td>
<td>79.70</td>
</tr>
<tr>
<td>Model A + CDi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWD</td>
<td>2.93</td>
<td>71.21</td>
</tr>
<tr>
<td>CDi</td>
<td>5.39</td>
<td>13.43</td>
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<tr>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Model B (NT-proBNP≥278pg/ml)</td>
<td>5.82</td>
<td>68.83</td>
</tr>
<tr>
<td>Model B + CDi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>4.88</td>
<td>13.82</td>
</tr>
<tr>
<td>CDi</td>
<td>5.64</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Model C (WHO class III)</td>
<td>10.01</td>
<td>70.29</td>
</tr>
<tr>
<td>Model C + CDi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO class</td>
<td>5.23</td>
<td>68.56</td>
</tr>
<tr>
<td>CDi</td>
<td>2.69</td>
<td>19.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Mouratoglou SA, et al. Hell J Cardiol 2019
## Risk assessment of PAH

<table>
<thead>
<tr>
<th>Determinants of prognosis* (estimated 1-year mortality)</th>
<th>Low risk &lt;5%</th>
<th>Intermediate risk 5–10%</th>
<th>High risk &gt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs of right heart failure</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>None</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Syncope</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO functional class</td>
<td>I, II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWD</td>
<td>&gt;440m</td>
<td></td>
<td></td>
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<tr>
<td>Cardiopulmonary exercise testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP plasma levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imaging (echocardiography, CMR imaging)</td>
<td>RA area &lt;18 cm²</td>
<td>RA area 18–26 cm²</td>
<td>RA area &gt;26 cm²</td>
</tr>
<tr>
<td></td>
<td>No pericardial effusion</td>
<td>No or minimal, pericardial effusion</td>
<td>Pericardial effusion</td>
</tr>
<tr>
<td>Haemodynamics</td>
<td>RAP &lt;8 mmHg</td>
<td>RAP 8–14 mmHg</td>
<td>RAP &gt;14 mmHg</td>
</tr>
<tr>
<td></td>
<td>CI ≥2.5 l/min/m²</td>
<td>CI 2.0–2.4 l/min/m²</td>
<td>CI &lt;2.0 l/min/m²</td>
</tr>
<tr>
<td></td>
<td>SvO₂ &gt;65%</td>
<td>SvO₂ 60–65%</td>
<td>SvO₂ &lt;60%</td>
</tr>
</tbody>
</table>

*No place for RV function?*
Serial CMR assessment

![Graph showing changes in RVEF and survival over time](Image)

- Changes in RVEF: p < 0.001
- Survival analysis: n = 39, n = 13
- Stable/increased RVEF vs Decreased RVEF
- p < 0.001
### Table 1: Relative reduction of RVLS and Hazard Ratio

<table>
<thead>
<tr>
<th>Author</th>
<th>Relative reduction of RVLS (%)</th>
<th>log(Hazard Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murata et al. 2016</td>
<td>5%</td>
<td>0.04879</td>
<td>0.04342</td>
<td>25.8%</td>
<td>1.05 [0.96, 1.14]</td>
</tr>
<tr>
<td>Glusca et al. 2012</td>
<td>6%</td>
<td>0.19885</td>
<td>0.14434</td>
<td>12.6%</td>
<td>1.22 [0.92, 1.62]</td>
</tr>
<tr>
<td>Haeck et al. 2012</td>
<td>19%</td>
<td>1.22378</td>
<td>0.53577</td>
<td>11.9%</td>
<td>3.40 [1.19, 9.72]</td>
</tr>
<tr>
<td>Kessel, van et al. 2016</td>
<td>19%</td>
<td>1.45861</td>
<td>0.69022</td>
<td>7.6%</td>
<td>4.30 [1.11, 16.63]</td>
</tr>
<tr>
<td>Park et al. 2015</td>
<td>31%</td>
<td>0.73716</td>
<td>0.35059</td>
<td>23.3%</td>
<td>2.09 [1.05, 4.15]</td>
</tr>
<tr>
<td>Sachdev et al. 2011</td>
<td>33%</td>
<td>0.69315</td>
<td>0.32446</td>
<td>25.9%</td>
<td>2.00 [1.06, 3.73]</td>
</tr>
</tbody>
</table>

**Total (95% CI):**

- Heterogeneity: Tau² = 0.05; Chi² = 5.27, df = 4 (P = 0.26); P = 24%
- Test for overall effect: Z = 5.45 (P < 0.0001)

**Figure 3** Forrest plot summarising the effect of a (relative) reduction of RVLS on all-cause mortality in PH patients. The red squares present the weighted effect size and the black lines the 95% CIs. The size of the red squares indicate the weight of the study. The black diamond presents the mean weighted HR.
Treatment Algorithm for Pulmonary Arterial Hypertension

TREATMENT NAİVE PATIENT

Treatment naïve patient

CCB Therapy (Table 17)

CCB Therapy (Table 17)

Vasoreactive

PAH confirmed by expert centre

Acute vasoreactivity test (IPAH/HPAH/DPAH only)

General measures (Table 15)

Supportive therapy (Table 16)

Non vasoreactive

Low or intermediate-risk (WHO-FC II-III)

Initial monotherapy (Table 18)

Initial oral combination (Table 19)

Patient already on treatment

Inadequate clinical response (Table 14)

Double or triple sequential combination (Table 20)

Inadequate clinical response (Table 14)

Consider listing for lung transplantation

Initial oral combination including i.v. PCA (Table 19)

High-risk (WHO-FC IV)

Consider referral for lung transplantation
Management of acute RV failure

Norepinephrine, 0.2–1.0 μg/kg/min
- Increases RV inotropy, systemic blood pressure, promotes positive ventricular interactions, restores coronary perfusion gradient
- Pulmonary vascular resistance is not seriously affected
- Excessive vasoconstriction may worsen tissue perfusion

Dobutamine, 2–20 μg/kg/min
- Increases RV inotropy, lowers filling pressures
- May aggravate arterial hypotension if used alone, without a vasopressor, especially if left heart failure present

Levosimendan, 0.1–0.2 μg/kg/min (no bolus in shock)
- Combines RV inotropy and pulmonary vasodilation;
- Favourably effects right ventricular-arterial uncoupling
- May aggravate arterial hypotension

Optimise cardiac output (inotropes such as dobutamine, milrinone)

Optimise blood pressure (vasopressors such as norepinephrine, vasopressin)

No realistic perspective of recovery or lung transplantation
• The RV initially adapts to the increased afterload by increasing its wall thickness and contractility (RV is coupled to the pulmonary arterial circulation)
• Most of the metrics of RV function used in clinical practice today are a reflection of ventriculoarterial coupling rather than contractility (load-independent measure)
• While RVEF is commonly used as an index of RV function, it is highly load dependent and does not reflect RV contractility
• Altered ventriculoarterial coupling occurs with increasing afterload, with some patients showing a better compensation or adaptability than others.
Acknowledgements
AHEPA University Hospital
Pulmonary Hypertension Unit

Thank you
Ventricular interdependence
Baseline and change in PVR and RVEF and outcome in PAH

Van de Veerdonk et al. JACC 2011
Presence of pericardial effusion

Right atrial area (per 5 cm² increase)

RV pressure estimates (per 10 mmHg increase)

TR severity

Estimated RA pressure

LV eccentricity index

Baggen VJM et al, Neth Heart J 2016