Pulmonary Arterial Hypertension: Assessment of disease’s severity

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Pulmonary Arterial Hypertension: The disease

Female 40 yrs
PAP = 50 mmHg
CI = 2.3 l/m/m2

NYHA Class III
6MWD = 380 m
PAH: natural history

CO exercise

FUNCTIONAL CLASS I

FUNCTIONAL CLASS II

FUNCTIONAL CLASS III

FUNCTIONAL CLASS IV

Symptoms

Time

CO

RAP

PAP

PVR

PAH: natural history
Prognosis of Idiopathic Pulmonary Arterial Hypertension (PAH) was poor

- Advanced lung cancer: 6 months
- WHO Class IV IPAH: 2.6 years
- Advanced colorectal cancer: 4.9 years
- Advanced breast cancer: 4.9 years
- WHO Class III IPAH: 4.9 years
- WHO Class I - II IPAH: 4.9 years
- Ischaemic cardiomyopathy: 7 years

References:
Specific approved drugs in PAH

Prostacyclin Derivatives

- Epoprostenol: IV
- Iloprost: inhaled
- Treprostinil: subcutaneous or IV

Endothelin Receptor Antagonists

- Bosentan: oral
- Ambrisentan: oral
- Sitaxsentan

Phosphodiesterase Type-5 Inhibitors

- Sildenafil: oral
The ESC/ERS 2010 therapeutic algorithm...

Treatment guided by Prognostic risk assessment?

It introduces the concept of Inadequate clinical response

Need for assessment during Follow-up
Our experience

Bosentan 125 mg bid

Run-in 62.5 mg bid

1 month - 1 month - 3 months - every 1/3 months

Clinical Evaluation
Walk-Test
Right cath study
ET-1 plasma levels
BNP plasma levels

Clinical Evaluation
Clinical worsening
Phone contact
Clinical Evaluation

Jan 2008
KM plot: patients without CW
KM plot: patients without CW

Oral therapies are not a cure for PAH! Need for a strict follow-up!

Breath-1  NEJM 2002
Mc Laughlin  ERJ 2005
Provencher  Thorax 2005
Prognostic indicators

- Clinical assessment
  - Symptoms
  - Clinical Signs
  - Rate of progression

- Exercise capacity
  - 6 minute walking test
  - CP exercise test

- RV function
  - Echo
  - MR heart

- Hemodynamics
  - Right Atrial Pressure
  - Cardiac Index

- Biomarkers
  - Troponin-T
  - BNP, Na, Creatinine
  - Uric Acid, PCR
Functional class & with survival

3-month epoprostenol

NYHA I or II
\( (n = 91) \)
\( p < 0.0001 \)

NYHA III or IV
\( (n = 75) \)

1-year epoprostenol


6-minute walk distance & survival

Cumulative survival vs. Time (months)

- **6-MWD ≥ 380 m**
- **6-MWD < 380 m**

*p = 0.0005*

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Subjects at risk (n)</th>
<th>6-MWD ≥ 380 m</th>
<th>6-MWD &lt; 380 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>78</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>12</td>
<td>71</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>24</td>
<td>56</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>36</td>
<td>41</td>
<td>16</td>
<td>16</td>
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<td>48</td>
<td>28</td>
<td>8</td>
<td>8</td>
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<tr>
<td>60</td>
<td>15</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>72</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>84</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>96</td>
<td>1</td>
<td>1</td>
<td>1</td>
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</tbody>
</table>

Cardiopulmonary exercise test

<table>
<thead>
<tr>
<th>Step</th>
<th>Variable</th>
<th>RR</th>
<th>P</th>
<th>Cumulative χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peak SBP, mm Hg</td>
<td>0.955</td>
<td>0.0046</td>
<td>27.6</td>
</tr>
<tr>
<td>2</td>
<td>Peak DBP, mm Hg</td>
<td>0.961</td>
<td>0.0495</td>
<td>33.7</td>
</tr>
<tr>
<td>3</td>
<td>Peak $\dot{V}O_2$, mL \cdot kg^{-1} \cdot min^{-1}$</td>
<td>0.814</td>
<td>0.0024</td>
<td>40.7</td>
</tr>
<tr>
<td>4</td>
<td>Uric acid, mg/dL</td>
<td>1.178</td>
<td>0.0037</td>
<td>44.7</td>
</tr>
</tbody>
</table>

Wessel R. Circulation. 2002;106:319-324
Prognostic Impact of Echocardiogram

<table>
<thead>
<tr>
<th>Significant multivariable predictors</th>
<th>HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pericardial effusion (Y/N)</td>
<td>4.38 (1.41–13.67)</td>
<td>0.011</td>
</tr>
<tr>
<td>Randomization to prostacyclin (Y/N)</td>
<td>0.25 (0.08–0.76)</td>
<td>0.014</td>
</tr>
<tr>
<td>6-min walk (500 ft)</td>
<td>0.56 (0.29–1.08)</td>
<td>0.082</td>
</tr>
<tr>
<td>Significant multivariable predictors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>of composite end point</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed venous O₂ (10%)</td>
<td>0.73 (0.56–0.94)</td>
<td>0.016</td>
</tr>
<tr>
<td>RA area index (5 cm²/m)</td>
<td>1.24 (0.96–1.61)</td>
<td>0.106</td>
</tr>
</tbody>
</table>

Raymond RJ. JACC 2002
Tei Index = \( \frac{(Dur \ IT - T \ Eiez \ VD)}{T \ Eiez \ VD} \)

![Diagram showing Tei Index calculation and survival analysis with 26 patients.](image)

Heart Magnetic Resonance & Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWT</td>
<td>0.28</td>
<td>0.09</td>
<td>1.18</td>
<td>0.087</td>
</tr>
<tr>
<td>Mean RA pressure</td>
<td>5.06</td>
<td>1.85</td>
<td>12.9</td>
<td>0.049</td>
</tr>
<tr>
<td>Mean PA pressure</td>
<td>0.81</td>
<td>0.21</td>
<td>3.08</td>
<td>0.745</td>
</tr>
<tr>
<td>RVRI</td>
<td>4.51</td>
<td>1.76</td>
<td>11.9</td>
<td>0.050</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>0.34</td>
<td>0.10</td>
<td>1.44</td>
<td>0.158</td>
</tr>
<tr>
<td>Stroke volume index</td>
<td>0.14</td>
<td>0.08</td>
<td>0.85</td>
<td>0.027</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.98</td>
<td>0.28</td>
<td>3.68</td>
<td>0.974</td>
</tr>
<tr>
<td>Mixed venous O₂ saturation</td>
<td>0.23</td>
<td>0.08</td>
<td>1.36</td>
<td>0.126</td>
</tr>
<tr>
<td>Cardiac index (MRI)</td>
<td>0.16</td>
<td>0.07</td>
<td>1.00</td>
<td>0.051</td>
</tr>
<tr>
<td>Stroke volume index (MRI)</td>
<td>0.10</td>
<td>0.04</td>
<td>0.59</td>
<td>0.006</td>
</tr>
<tr>
<td>RV mass index</td>
<td>2.12</td>
<td>0.58</td>
<td>7.79</td>
<td>0.274</td>
</tr>
<tr>
<td>LV mass index</td>
<td>0.08</td>
<td>0.03</td>
<td>1.54</td>
<td>0.055</td>
</tr>
<tr>
<td>RV wall thickness</td>
<td>2.84</td>
<td>0.78</td>
<td>7.25</td>
<td>0.197</td>
</tr>
<tr>
<td>RV wall thickness</td>
<td>0.54</td>
<td>0.13</td>
<td>2.31</td>
<td>0.410</td>
</tr>
<tr>
<td>LV EF</td>
<td>0.12</td>
<td>0.05</td>
<td>0.73</td>
<td>0.016</td>
</tr>
<tr>
<td>LV EF</td>
<td>0.55</td>
<td>0.15</td>
<td>2.19</td>
<td>0.534</td>
</tr>
<tr>
<td>RV EDV (ml)</td>
<td>6.69</td>
<td>1.91</td>
<td>16.4</td>
<td>0.037</td>
</tr>
<tr>
<td>LV EDV (ml)</td>
<td>0.19</td>
<td>0.08</td>
<td>0.77</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Univariate Analysis of the Change in Variables, Including Magnetic Resonance Imaging Data After 1-Year Follow-Up as a Potential Predictor of Mortality in IPAH

Haemodynamic abnormalities and prognosis

Median survival (months)

- Mean PAP:
  - < 55 mmHg: 50 months
  - ≥ 85 mmHg: 10 months

- Mean RAP:
  - < 10 mmHg: 50 months
  - ≥ 20 mmHg: 10 months

- Mean CI:
  - ≥ 4 l/min/m$^2$: 50 months
  - < 2 l/min/m$^2$: 10 months

Biomarkers

Different mechanism:
- Marker of RV overload  (BNP, NT-proBNP)
- Marker of myocardial injury  (Troponin)
- Marker of Systemic inflammation  (C-reactive protein)
Brain natriuretic peptide (BNP)

Baseline BNP

Follow-up BNP

Survival rate (%)

Time (months)

BNP <150 pg/ml

BNP ≥150 pg/ml

BNP <180 pg/ml

BNP ≥180 pg/ml

Troponin I and troponin T

Subjects at risk, n

Time (months)

Cumulative survival

0.0
0.2
0.4
0.6
0.8
1.0

$p = 0.0005$

$p = 0.005$

$p = 0.001$

$cTnT(-)$

$cTnT(+)$$

C Reactive Protein

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>Monthly</th>
<th>6 Months</th>
<th>Clinical judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical evaluation</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking test</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood gas analysis</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Test</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Echo Doppler</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cardiopulm. test</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hemodynamic</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>BNP(?)</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
A shift of strategy!
We do not have to wait for deterioration,
but combine treatments if the patient does not
reach clinical meaningful targets
Treat to goals 2005

- 6MWT > 380 mt
- Peak VO2 10,4 ml/kg/m
- Exerc. BP > 120 mmHg

Diagnosis of PAH Vasoreactivity test negative NYHA III or IV

Baseline examination and 2–6 monthly re-evaluation to assess treatment goals (6-min walk distance >380 m, peak VO₂ >10.4 mL·min⁻¹·kg⁻¹, peak systolic blood pressure >120 mmHg during exercise)

- Treatment goals not met
  - First-line treatment bosentan
    - Addition of sildenafil
      - Addition of inhaled iloprost
        - Transition from inhaled to intravenous iloprost
          - Highly urgent lung transplantation
  - Treatment continued

- Treatment goals met
  - Treatment continued

Effect of “treatment to goals” on survival

Treatment group vs historical control group, \( p=0.011 \)
Treatment group vs expected survival, \( p<0.001 \) for all time points

Subjects at risk (\( n \))
- Treatment group: 89, 83, 69, 61, 46, 43, 37
- Historical control group: 67, 64, 47, 38, 31, 23, 20

Months
- 0, 6, 12, 18, 24, 30, 36

Cumulative survival (IPAH)
- First-line bosentan
- Addition of sildenafil/iloprost 2002-2004
- Historical control group 1999-2001
- Expected survival

## ESC/ERS 2009 PAH guidelines

<table>
<thead>
<tr>
<th>Better prognosis</th>
<th>Determinants of prognosis</th>
<th>Worse prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Clinical evidence of RV failure</td>
<td>Yes</td>
</tr>
<tr>
<td>Slow</td>
<td>Rate of progression of symptoms</td>
<td>Rapid</td>
</tr>
<tr>
<td>No</td>
<td>Syncope</td>
<td>Yes</td>
</tr>
<tr>
<td>I, II</td>
<td>WHO-FC</td>
<td>IV</td>
</tr>
<tr>
<td>Longer (&gt;500 m)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6MWT</td>
<td>Shorter (&lt;300 m)</td>
</tr>
<tr>
<td>Peak O&lt;sub&gt;2&lt;/sub&gt; consumption &gt;15 mL/min/kg</td>
<td>Cardio-pulmonary exercise testing</td>
<td>Peak O&lt;sub&gt;2&lt;/sub&gt; consumption &lt;12 mL/min/kg</td>
</tr>
<tr>
<td>Normal or near-normal</td>
<td>BNP/NT-proBNP plasma levels</td>
<td>Very elevated and rising</td>
</tr>
<tr>
<td>No pericardial effusion TAPSE&lt;sup&gt;b&lt;/sup&gt; &gt;2.0 cm</td>
<td>Echocardiographic findings&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Pericardial effusion TAPSE&lt;sup&gt;b&lt;/sup&gt; &lt;1.5 cm</td>
</tr>
<tr>
<td>RAP &lt;8 mmHg and CI &gt;2.5 L/min/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Haemodynamics</td>
<td>RAP &gt;15 mmHg or CI ≤2.0 L/min/m&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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<sup>a</sup> Peak exercise or 6MWD performed by the patient to assess functional capacity.

<sup>b</sup> Measurements performed at rest and 6MWT.

Are these criteria applicable to SSc-PAH?
Registry data of bosentan therapy in PAH-SSc

- Royal Free Hospital registry-based evaluation of the impact of bosentan on exercise capacity, and survival in patients in class III and class IV PAH and SSc

- Patients with PAH-SSc treated with bosentan as per BREATHE-1 protocol were compared to PH-SSc BREATHE-1 eligible control patients

Are these criteria applicable to SSc-PAH?

SSc PAH patients have:
- a worse effort capacity
- a better cardiac index compared to Idiopathic PAH

<table>
<thead>
<tr>
<th></th>
<th>Current treatment era (n=45)</th>
<th>History control (n=44)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMWT distance (m)</td>
<td>207 (0–538)</td>
<td>179 (0–471)</td>
<td>0.1</td>
</tr>
<tr>
<td>mRAP (mm Hg)</td>
<td>8 (6.1)</td>
<td>7 (4.4)</td>
<td>NS</td>
</tr>
<tr>
<td>mPAP (mm Hg)</td>
<td>40 (11.8)</td>
<td>40 (11.4)</td>
<td>NS</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>102 (18)</td>
<td>95 (15)</td>
<td>NS</td>
</tr>
<tr>
<td>PVR (dyn·s·cm⁻⁵)</td>
<td>613 (345)</td>
<td>597 (359)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.6 (0.7)</td>
<td>2.7 (0.9)</td>
<td>NS</td>
</tr>
<tr>
<td>WHO functional class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>26 (58%)</td>
<td>36 (77%)</td>
<td>0.054</td>
</tr>
<tr>
<td>IV</td>
<td>19 (42%)</td>
<td>11 (23%)</td>
<td></td>
</tr>
<tr>
<td>Scleroderma subset (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>43 (96%)</td>
<td>34 (72%)</td>
<td>0.0026</td>
</tr>
<tr>
<td>Diffuse</td>
<td>2 (4%)</td>
<td>13 (28%)</td>
<td></td>
</tr>
<tr>
<td>Patients with pulmonary fibrosis</td>
<td>14 (31%)</td>
<td>22 (46%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Conclusions

• Assessment of PAH severity is important at every stage of the disease:
  – Baseline (decision making: which drug is indicated?)
  – Response to treatment
  – Adjustment of treatment regimen

• A combination of end-points is recommended when evaluating disease severity and progression (NYHA, 6-minWT, echo, hemodynamics, biomarkers?)
PH Unit
La Sapienza, University of Rome
Head Carmine Dario Vizza

PH clinicians (Cardiology ward, CCU, consultation & outpatients management):

- **Senior Cardiologists**: Dr Vizza, Dr Badagliacca Dr. Poscia
- **Fellows**: Dr. Nona, Dr. Crescenzi
- **In Training**: Dr Gambardella, Dr. Pezzuto, Dr Papa, Dr Marcon

---

**Echo Lab**
- Dr. Sciomer
- Dr. Badagliacca

**PFTs-CPX Lab**
- Prof. Palange
- Dott. Valli

**CT & RNM Lab**
- Dott. Carbone
- Dott. Francone

**Right Cath Lab**
- Dott. Mancone
- Dott. Colantoni

---

**Reumathologists**
- Prof Valesini
- Prof.Ricciere

**Liver Transplant Unit**
- Prof. Rossi
- Prof. Corradini

**HIV clinic**
- Prof.Vullo

**Pulmonologists**
- Prof. Parola

**Lung Transplant Program**
- Prof.Coloni
- Prof.Venuta
Back-up slides