How to manage IPAH in an emergency: PAH with frequent syncope

Jean-Luc Vachiéry

Pulmonary Vascular Diseases and Heart Failure Clinic
Hôpital Universitaire Erasme
Université Libre de Bruxelles
Belgium
Name of Companies with which relationship exists:

Actelion Pharmaceuticals, BayerShering, Eli Lilly, GlaxoSmithKline, Pfizer, United Therapeutics

Nature of Relationship:

Consultant, Honoraria, Advisory Board Member, Research Chair
IM, woman born in 1972

No relevant medical history
Housekeeper, no sports
Married no children

April 2009

• Lost consciousness while feeling tired, mildly dyspnoeic on exertion (walking uphill, > 2 flights of stairs) for 2 weeks
• No significant impairment in daily activities
• Another episode of “lightheadedness” while shopping in May

September 2010

• Episode of syncope at top of the stairs, carrying laundry
• Referred to outpatient clinic with evidence of RV hypertrophy and suspicion of PH
## Diagnosis of Idiopathic PAH, non responder to NO

<table>
<thead>
<tr>
<th>Determinant of prognosis</th>
<th>Better prognosis</th>
<th>Grey zone</th>
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</tr>
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<tbody>
<tr>
<td>Clinical evidence of RHF</td>
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<tr>
<td>Syncope</td>
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<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>WHO FC</td>
<td>I-II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWT</td>
<td>Longer (&gt;500m)</td>
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<td>Haemodynamics</td>
<td>RAP &lt; 8 mmHg and CI &gt; 2.5 l’/m²</td>
<td></td>
<td>Pericardial effusion, TAPSE &lt; 15 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RAP &gt; 15 or CI &lt; 2 l’/m²</td>
</tr>
</tbody>
</table>

Questions raised at time of diagnosis

• Syncope: a common initial presentation?

• Impact on NYHA classification?

• Role in the choice of 1st line therapy?
### Syncope and NYHA FC at time of diagnosis in registries

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Distribution</strong></td>
<td>National (USA)</td>
<td>1 centre (Chicago)</td>
<td>National (Swiss)</td>
<td>National (France)</td>
<td>3 centres (China)</td>
<td>National (USA)</td>
</tr>
<tr>
<td><strong>Patients, n</strong></td>
<td>187</td>
<td>245</td>
<td>192</td>
<td>674</td>
<td>72</td>
<td>2716</td>
</tr>
<tr>
<td><strong>Syncope, %</strong></td>
<td>13</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>26</td>
<td>- (12*)</td>
</tr>
<tr>
<td><strong>WHO FC, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>29</td>
<td>20</td>
<td>12</td>
<td>24</td>
<td>37</td>
<td>37.8</td>
</tr>
<tr>
<td>III</td>
<td>62</td>
<td>63</td>
<td>44</td>
<td>48.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>71 III/IV</td>
<td>80 III/IV</td>
<td>25</td>
<td>12</td>
<td>17</td>
<td>5.5</td>
</tr>
</tbody>
</table>

> 10 % of patients with PAH present syncope at diagnosis
I. Patients with PH without limitation of physical activity. Ordinary activity does not cause undue dyspnoea or fatigue, chest pain or **near syncope**

II. Patients with PH resulting in slight limitation of physical activity. Comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or **near syncope**

III. Patients with PH resulting in marked limitation. Less than ordinary activity causes undue fatigue or dyspnoea, chest pain or **near syncope**

IV. Patients with PH with inability to carry out any physical activity. Signs of right heart failure. **Syncope***

* Although not mentionned explicitely
NYHA FC at diagnosis has an impact on outcome in IPAH
Survival rate of patients in FC II after 3 years is < 85 %
Longer duration of symptoms  
Less severe haemodynamics  
lower RAP and mPAP  
higher CO  
lower PVR  
Less severe disease  
more FC II  
less RV failure  
better 6MWD  
Present more syncope

Long-Term Response to Calcium Channel Blockers in Idiopathic Pulmonary Arterial Hypertension

Olivier Sitbon, MD; Marc Humbert, MD, PhD; Xavier Jaïs, MD; Vincent Ioos, MD; Abdul M. Hamid, MD; Steeve Provencher, MD; Gilles Garcia, MD; Florence Parent, MD; Philippe Hervé, MD; Gérald Simonneau, MD

TABLE 1. Clinical Characteristics, Baseline Hemodynamics, and Exercise Capacity of the Studied Patient Sample

|                                | All Patients (n=557) | Acute Responders (n=70) | Non–Acute Responders (n=487) | P*
|--------------------------------|----------------------|-------------------------|-------------------------------|-----
| Age at diagnosis, y            | 45±15                | 44±16                   | 45±15                         | 0.74
| Male:female, %                 | 36:65                | 34:66                   | 35:65                         | 0.9
| Onset of symptoms, mo          | 20±31                | 29±38                   | 19±29                         | 0.015
| Raynaud's phenomenon, %        | 14                   | 16                      | 14                            | 0.8
| Antinuclear antibody titer >1/80, % | 13                | 16                      | 10                            | 0.15
| History of syncope, %          | 37                   | 54                      | 36                            | <0.010
| History of right heart failure, %| 33                  | 19                      | 35                            | <0.010
| NYHA class I-II:III-IV, %      | 19:81                | 47:53                   | 15:85                         | <0.001
| Six-minute walk distance, m    | 287±139 (n=351)      | 346±130 (n=43)          | 279±139 (n=308)               | 0.003
| Baseline hemodynamics          |                      |                        |                               |     
| Mean RAP, mm Hg                | 10±5                 | 7±4                     | 11±5                          | <0.001
| Mean PAP, mm Hg                | 61±14                | 57±12                   | 62±14                         | 0.007
| Mean PWP, mm Hg                | 9±3                  | 8±3                     | 9±3                           | 0.020
| Cardiac output, L·min⁻¹         | 3.9±1.2              | 4.5±1.4                 | 3.7±1.1                       | <0.001
| PVR, Wood units                | 14.8±6.5             | 12.2±5.3                | 15.3±6.6                      | <0.001
| Svo₂₂, %                       | 59±10                | 66±9                    | 58±10                         | <0.001

RAP indicates right atrial pressure.
*Comparison between acute responders and nonresponders (Student t or χ² test, as appropriate).
Survival in Childhood Pulmonary Arterial Hypertension
Insights From the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management

- **N=216 patients with PAH included in the REVEAL registry**
- Dyspnoea is the most common presenting symptom (54%)
- Presyncope/syncope was present in 24%
  - IPAH/heritable, 36%
  - PAH-CHD, 4%
- Not identified as a risk factor for increased mortality


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**RETRACTION NOTICE**


Rachel J. Le, MD, Eric R. Fenstad, MD, Hilal Maradit-Kremers, MD, Robert B. McCully, MD, Robert P. Frantz, MD, Michael D. McGoon, MD, Garvan C. Kane, MD, PhD.

Department of Medicine, Mayo Clinic, Rochester, Minnesota; and the Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota.

Available online August 8, 2011.
First-line therapy and outcome

**September 2010**

- IPAH, non responder, NYHA III-IV, intermediate prognosis
- Choice of first-line oral therapy (ET-1 receptor antagonist)

<table>
<thead>
<tr>
<th>Test</th>
<th>At diagnosis</th>
<th>January 2011</th>
<th>Change</th>
</tr>
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<tbody>
<tr>
<td>NYHA FC</td>
<td>III-IV</td>
<td>II - III</td>
<td>+</td>
</tr>
<tr>
<td>6MWT (Borg)</td>
<td>380 m (8)</td>
<td>410 m (8)</td>
<td>=</td>
</tr>
<tr>
<td>Syncope</td>
<td>Yes</td>
<td>No</td>
<td>+</td>
</tr>
<tr>
<td>Peak VO2 (ml/kg/’)</td>
<td>13</td>
<td>13.8</td>
<td>+</td>
</tr>
<tr>
<td>Workload (W)</td>
<td>40</td>
<td>60</td>
<td>+</td>
</tr>
<tr>
<td>VE/VCO2 slope</td>
<td>56</td>
<td>55</td>
<td>=</td>
</tr>
<tr>
<td>NT-pro BNP (pg/ml)</td>
<td>1,265</td>
<td>780</td>
<td>+</td>
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Should we be satisfied with this evaluation under therapy?
### After first evaluation under monotherapy

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March 2011 (scheduled for RHC – insufficient response)

- 2 episodes of syncope at low level of exercise

IPAH on ERA – recurrent syncope – high RAP and low CI

\[ \text{mPAP} 49 \text{ mmHg} \]
\[ \text{RAP} 20 \text{ mmHg} \]
\[ \text{CO} 3.0 \text{ l/min} – \text{CI} 1.7 \]
\[ \text{PVR} 15 \text{ WU} \]
Questions raised after first follow up assessment

• How can the syncope(s) be explained?
• What are the therapeutic options?
Haemodynamic response to increased RV afterload

Pulmonary hypertension
Increased RV afterload

Increased Wall tension
RV hypertrophy
RV ischemia
Decreased RV output

RV dilatation
Limit preload reserve
Tricuspid regurg
Septal shift
Altered LV filling
Decreased LV output

Adapted from Chemla Eur Respir J 2002
Mechanism of syncope in PAH

**Loss of ventricular adaptation to afterload**

- Decreased RV output and RV/LV interdependence
- Uncoupling between RV and pulmonary circulation
- Unmet demand to increase CO during exercise
- Drop in systemic pressure due to abrupt decrease in SV

**Other (uncommon) contributing factors**

- Arrhythmias
- RV and/or LV ischemia
  - Subendocardial microcirculation
  - Dynamic occlusion of LAD due to PA dilatation
- Severe PA dilatation
IPAH, recurrent syncope on ERA

**March 2011**

- Aggressive diuresis and temporary inotropic support
- Parenteral prostacyclin, evaluation for transplantation

<table>
<thead>
<tr>
<th>Test</th>
<th>Diagnosis</th>
<th>March 2011 ERA</th>
<th>July 2011 ERA+PGI₂</th>
<th>Change</th>
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<tbody>
<tr>
<td>NYHA FC</td>
<td>III-IV</td>
<td>III-IV</td>
<td>II-III</td>
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<td>-</td>
<td>430 (8)</td>
<td>+</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.8</td>
<td>1.7</td>
<td>2.9</td>
<td>=</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>4</td>
<td>18</td>
<td>10</td>
<td>+</td>
</tr>
<tr>
<td>PCWP</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>=</td>
</tr>
<tr>
<td>NT-pro BNP (pg/ml)</td>
<td>1,265</td>
<td>2,160</td>
<td>880</td>
<td>+</td>
</tr>
</tbody>
</table>

**January 2012 (despite initiation of PDE5i)**

- Palpitations, 3 episodes of syncope within a month (unrelated)
Questions raised under triple combo therapy

• Can this be triggered by arrhythmia?

• Isn’t it time for intervention?
Arrhythmias in PAH – Atrial fibrillation (AF) + flutter (Afl)

- Morphological changes
  RV and RA hypertrophy (substrate for SVA)
  RA dilatation (cavo tricuspid isthmus)
  RA/LA interdependence through septum

- Sympathetic nervous system overactivation*

Atrial flutter and fibrillation in patients with pulmonary hypertension

Karen M. Olsson a,1, Nils P. Nickel a,1, Jörn Tongers b, Marius M. Hoeper a,*

a Department of Respiratory Medicine, Hannover Medical School, Hannover, Germany
b Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany

- N=239 – n=48 (20%) equally distributed between AF and Afl
- Treatment depending on clinical presentation
- Risk higher in age, higher RAP, mPAP, NT proBNP and lower CI
- 83% clinical deterioration (RVF, dyspnoea, weight gain)
- Syncope was only present in 1 patient

Olson K et al. Int J Cardiol (2012), doi:10.1016/j.ijcard.2012.06.024
Strategy to manage arrhythmias in PAH

Clinical instability (RVF, hypotension)

Yes
- Treat aggressively
  - Amiodarone IV/oral
  - Electrical CV

No
- Amiodarone oral
  - Consider oral AC
  - AF: electrical CV
  - Afl: RF ablation

• Consider TEE in case of AF if unknown onset
• Avoid other antiarrhythmic drugs
• SR restored in 88% Afl (67% RFA) and 67% AF (75% ECV)*

* Olson K et al. Int J Cardiol (2012), doi:10.1016/j.ijcard.2012.06.024
<table>
<thead>
<tr>
<th>RecommendationEvidence</th>
<th>WHO FC II</th>
<th>WHO FC III</th>
<th>WHO FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-A</td>
<td>Ambrisentan, bosentan, sildenafil</td>
<td>Ambrisentan, bosentan, sildenafil, <em>epoprostenol iv</em>, <em>iloprost inhaled</em></td>
<td>Epoprostenol iv</td>
</tr>
<tr>
<td>I-B</td>
<td>Tadalafil</td>
<td>Tadalafil, <em>treprostinil sc</em>, inhaled</td>
<td>Ambrisentan, bosentan, sildenafil, <em>iloprost</em>, <em>treprostinil</em>, initial combo</td>
</tr>
<tr>
<td>IIa-C</td>
<td><em>Iloprost iv</em>, <em>treprostinil iv</em></td>
<td><em>Iloprost iv</em>, <em>treprostinil iv</em></td>
<td></td>
</tr>
<tr>
<td>IIb-B</td>
<td>beraprost</td>
<td></td>
<td></td>
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</table>

**Inadequate clinical response**

**Sequential combination therapy (IIa-B)**

- **ERA**
  - **Prostanoid** — **PDE5-i**

**Atrial septostomy (I-C) and/or Lung transplantation (I-C)**

Adapted from Galiè et al. Eur Heart J 2009; 30: 2493–2537
Why is septostomy beneficial?

Atrial Septostomy
Right-to-left shunting

- RV diastolic pressure
- RA pressure

- RV wall stress
- RV ischemia?

- Venous return

- RV/LV interdependence

- RV microcirculation?

- Sympathetic overactivation

- Cardiac output

- $O_2$ transport

Grade blade-balloon septostomy

- Gradual dilatation procedure
- Stepwise haemodynamic approach
- Two main objectives:

**LV filling pressure (Pcwp or Pla)**

- $\leq$ two-fold increase vs base
- Kept $<$ 15 mmHg

**Systemic oxygen saturation**

- $\pm$ 10 % drop vs base
- Kept around 85 %
Introducer inserted across the interatrial septum

Dilatation post septostomy with an 8 mm balloon
Fenestrated Amplatzer® occluder \(^1\-^3\)
Potential sizing by stent procedure \(^3\)

Limited experience so far (n=17)
Advantage: to avoid secondary occlusion

<table>
<thead>
<tr>
<th>Characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>28 ± 17</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
</tr>
<tr>
<td>IPAH</td>
<td>82%</td>
</tr>
<tr>
<td>PAH due to corrected L-R shunt</td>
<td>8%</td>
</tr>
<tr>
<td>PAH due to connective tissue disease</td>
<td>5%</td>
</tr>
<tr>
<td>CTEPH</td>
<td>3%</td>
</tr>
<tr>
<td>Other cause</td>
<td>3%</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>3.6±0.4</td>
</tr>
</tbody>
</table>

| Main indication for intervention       |       |
| Right heart failure                    | 43%   |
| Syncope                                | 38%   |
| Association of both previous indication| 19%   |
| Bridge to transplantation              | 14%   |

| Medical therapy at time of intervention| n = 93 (43%) |
| Intravenous prostanoids                | 61%    |
| Inhaled or subcutaneous prostacyclin   | 8%     |
| Single oral therapy                    | 34%    |
| Combined therapy (any combination)     | 11%    |

BAS – survival improvement?

Table 2. Survival after AS

<table>
<thead>
<tr>
<th>Study</th>
<th>Number (procedures)</th>
<th>1-year</th>
<th>2-year</th>
<th>3-year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>predicted</td>
<td>observed</td>
<td>predicted</td>
</tr>
<tr>
<td>Kerstein et al. [28]</td>
<td>13 (13)</td>
<td>62</td>
<td>86</td>
<td>48</td>
</tr>
<tr>
<td>Law et al. [26]</td>
<td>43 (46)</td>
<td>68</td>
<td>84</td>
<td>55</td>
</tr>
<tr>
<td>Sandoval et al. [23]</td>
<td>34 (50)</td>
<td>65</td>
<td>90</td>
<td>52</td>
</tr>
</tbody>
</table>

Survival values are percentages.


![Graphs showing survival rates after AS and AS + PAH therapy.](image-url)
### Indications

- Failure of medical therapy
- Persistent RV failure and/or syncope
- Clinical deterioration despite rapid treatment escalation
- Absence of therapeutic alternative or refusal of appropriate medical therapy
- Bridge-to-transplantation

### Contra indications

- Right atrial pressure > 20 mmHg and/or Left atrial pressure > 18 mmHg
- SaO₂ < 90% on room air
- Severe, decompensated right heart failure
- Permanent inotropic or respiratory support
- End-stage disease

<table>
<thead>
<tr>
<th>Environment</th>
<th>Only in specialised/expert centres (PAH and transeptal approach)</th>
</tr>
</thead>
</table>
| **Patient preparation** | • Improvement in cardiac function and filling pressures (diuretics and/or inotropes)  
  • Correction of metabolic and haematological disorders (anemia, thrombocytopenia) |
| **During the procedure** | • Oxygen support  
  • Light sedation, anxiety control  
  • Continuous monitoring of pressures (systemic and RAP) and SaO₂  
  • SaO₂ < 10% vs baseline and > 85%  
  • Stepwise procedure and increase balloon size |
| **After the procedure** | • Oxygen support for SaO₂ > 90%  
  • Consider transfusion |

Syncope is frequent as the first symptom of IPAH in children and in responders to vasoreactivity challenge.

In most cases, it results from inadequate adaptation of the RV to an increased demand in CO during exercise.

Persistent syncope during FU should be considered as deterioration, requiring reassessment + therapy escalation.

Although not associated with syncope, arrhythmias are common in PAH and should be treated aggressively (RFA for Afl and amiodarone+electrical cardioversion for AF).

Atrial septostomy can be offered to treat syncope, maybe at earlier stage of disease.