3 Definitions and Classifications and Particularities of Different PAH Subgroups

<table>
<thead>
<tr>
<th></th>
<th>Name</th>
<th>City</th>
<th>Country</th>
<th>Email</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Gérald Simonneau</td>
<td>Clermont</td>
<td>FRANCE</td>
<td><a href="mailto:gerald.simonneau@abc.aphp.fr">gerald.simonneau@abc.aphp.fr</a></td>
<td>Chair</td>
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<tr>
<td>2.</td>
<td>Rogerio Souza</td>
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<td><a href="mailto:rgrdzn@gmail.com">rgrdzn@gmail.com</a></td>
<td>Co-chair</td>
</tr>
<tr>
<td>3.</td>
<td>Ian Adatia</td>
<td>Edmonton</td>
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<td><a href="mailto:iadatia@ualberta.ca">iadatia@ualberta.ca</a></td>
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</tr>
<tr>
<td>4.</td>
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<tr>
<td>5.</td>
<td>Chris Denton</td>
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<td>Mike Gatzoulis</td>
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<td><a href="mailto:M.Gatzoulis@bht.nhs.uk">M.Gatzoulis@bht.nhs.uk</a></td>
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</tr>
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<td>7.</td>
<td>Ardeschir Ghofrani</td>
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<td></td>
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<td>8.</td>
<td>Miguel Angel Gómez Sánchez</td>
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<td></td>
</tr>
<tr>
<td>9.</td>
<td>Krishna Kumar</td>
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<td></td>
</tr>
<tr>
<td>10.</td>
<td>Michael Landzberg</td>
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<td><a href="mailto:Mike.Landzberg@CARDIO.CHBOSTON.ORG">Mike.Landzberg@CARDIO.CHBOSTON.ORG</a></td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>Roberto Machado</td>
<td>Chicago IL</td>
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<td><a href="mailto:machado@uiuc.edu">machado@uiuc.edu</a></td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>Horst Olschewski</td>
<td>Graz</td>
<td>AUSTRIA</td>
<td><a href="mailto:Horst.Olschewski@klinikum-graz.at">Horst.Olschewski@klinikum-graz.at</a>; <a href="mailto:horst.olschewski@meduniv.graz.at">horst.olschewski@meduniv.graz.at</a></td>
<td></td>
</tr>
<tr>
<td>13.</td>
<td>Ivan Robbins</td>
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<td><a href="mailto:ivan.robbins@Vanderbilt.Edu">ivan.robbins@Vanderbilt.Edu</a></td>
<td></td>
</tr>
</tbody>
</table>
• A. Should we include rest PVR in the definition of PH? how do we define and handle “borderline” PH? Should PVR & PAP on exercise be reintroduced in the definition?

• B. PAH associated with CHD in adults

• C. Are there novel drugs and toxins inducing PAH?

• D. Which changes in group 5? New groups identified or previous one to shift to another PH? group? Should we maintain sickle cell disease PAH in group 1?
• Should we include rest PVR in the definition of PH?

• how do we define and handle “borderline” PH?

• Should PVR & PAP on exercise be reintroduced in the definition?
Should we include rest PVR in the definition of PH?

Definition of PAH: mean PAP ≥ 25 mmHg at rest
or > 30 mm Hg with exercise
PCWP ≤ 15 mmHg  PVR > 3 WU (240 dyn.sec.cm⁻⁵)

5th WS  D. Badesch et al (JACC 2009)
simplification of PH definition as follows:
• Exercise and PVR criteria should be eliminated
• PH is defined as resting m PAP ≥25 mmHg
• mPAP <20 mmHg should be considered normal
• Further studies are needed to determine the natural history of patients with m PAP 21 to 24 mm Hg
• Should we include rest PVR in the definition of PH?

**Table 3**: Haemodynamic definitions of pulmonary hypertension

<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics</th>
<th>Clinical group(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary hypertension (PH)</td>
<td>Mean PAP ≥ 25 mmHg</td>
<td>All</td>
</tr>
<tr>
<td>Pre-capillary PH</td>
<td>Mean PAP ≥ 25 mmHg</td>
<td>1. Pulmonary arterial hypertension</td>
</tr>
<tr>
<td></td>
<td>PWP ≤ 15 mmHg</td>
<td>3. PH due to lung diseases</td>
</tr>
<tr>
<td></td>
<td>CO normal or reducedf</td>
<td>4. Chronic thromboembolic PH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. PH with unclear and/or multifactorial mechanisms</td>
</tr>
<tr>
<td>Post-capillary PH</td>
<td>Mean PAP ≥ 25 mmHg</td>
<td>2. PH due to left heart disease</td>
</tr>
<tr>
<td></td>
<td>PWP &gt; 15 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CO normal or reducedf</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Passive TPG ≤ 12 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reactive TPG &gt; 12 mmHg</td>
<td></td>
</tr>
</tbody>
</table>

*a* All values measured at rest

ESC & ERS Guidelines 2009
A1. Should we include PVR at rest in the definition of PH

- The definition of PH should be a simple and pragmatic and should be changed only for very important reasons.

- Due to the lack of new pertinent informations, it seems reasonable to keep the Dana Point definition of PH unchanged (PAPm ≥25 mmHg at rest) and to not include rest PVR in the definition of PH in agreement with the TF 6 (Marius Hoeper, Chair)
On Pulmonary Vascular Resistance: The Need For More Precise Definition

MAURICE McFREGOR, MD, and ALLAN SNIDERMAN, MD

In summary, the ratio of PA pressure with or without subtraction of LA pressure, divided by flow, has traditionally been understood to indicate resistance. This is misleading because this ratio will change with changes in flow, without there being any change in the forces opposing flow.

January 1, 1985  THE AMERICAN JOURNAL OF CARDIOLOGY
Pulmonary haemodynamics in liver cirrhosis

- N = 178
- M/F = 110/66
- No β-blocker
- PAPm < 25 mmHg

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP, mmHg</td>
<td>5.7</td>
<td>2.7</td>
<td>[0 – 15]</td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>15.5</td>
<td>3.4</td>
<td>[6 – 24]</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>9.2</td>
<td>3.1</td>
<td>[2 – 17]</td>
</tr>
<tr>
<td>CO, L.min⁻¹</td>
<td>8.25</td>
<td>2.13</td>
<td>[4.45 – 16.37]</td>
</tr>
<tr>
<td>CI, L.min⁻¹.m⁻²</td>
<td>4.64</td>
<td>1.11</td>
<td>[2.92 – 9.21]</td>
</tr>
<tr>
<td>PVR, dyn.s.cm⁻⁵</td>
<td>65</td>
<td>28</td>
<td>[10 – 157]</td>
</tr>
</tbody>
</table>

Eur Respir J 2004;
<table>
<thead>
<tr>
<th>No of Patients (Percentage)</th>
<th>Pre-capillary PAH</th>
<th>Post-capillary PH</th>
<th>No PH on RHC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11 (2.9%)</td>
<td>13 (3.3%)</td>
<td>72 (18.7%)</td>
</tr>
<tr>
<td>mPAP (mm Hg)</td>
<td>28±4</td>
<td>32±7</td>
<td>19±3</td>
</tr>
<tr>
<td>sPAP (mm Hg)</td>
<td>43±7</td>
<td>45±8</td>
<td>28±4</td>
</tr>
<tr>
<td>dPAP (mm Hg)</td>
<td>15±5</td>
<td>22±6</td>
<td>12±3</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>5±2</td>
<td>13±5</td>
<td>7±2</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>10±3</td>
<td>21±5</td>
<td>11±3</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>8.2±1.6</td>
<td>9.1±2.1</td>
<td>8.4±2.1</td>
</tr>
<tr>
<td>PVR (dyn.s.cm⁻⁵)</td>
<td>178±55</td>
<td>104±26</td>
<td>72±26</td>
</tr>
</tbody>
</table>

New Engl J Med 2011
A2 how do we define and handle “borderline” PH?

- The upper limit of a normal PAPm is 20 mmHg.
- PH is defined as mean PAP ≥ 25 mmHg
- For patients with a mean PAP between 21 and 24 mm Hg who not fulfill the criteria for manifest PH It has been proposed to use the term of “borderline” PH
- “borderline PH” is frequently observed in Group 2 and 3, however the clinical meaningful of this observation is unknown and has no therapeutic implications
- “Borderline PH” is also frequently observed in scleroderma patients screened for PH. A substantial number of these patients seem to develop manifest PAH in the follow-up. We recommend today to use the term of “borderline” PH only in scleroderma patients
Long-term Follow-up of Borderline PH in Sleroderma

Royal Free cohort – natural history of borderline PH (mPAP 21-24 mm Hg at first RHC)

Kaplan-Meier plots of time to the development of pulmonary hypertension confirmed at repeat RHC. The borderline pulmonary hypertension group have significantly increased risk (p=0.001, log-rank test) compared with the normal group.

<table>
<thead>
<tr>
<th>(months)</th>
<th>Normal</th>
<th>Borderline</th>
</tr>
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<tbody>
<tr>
<td>at risk</td>
<td>142</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>126</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>68</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>13</td>
</tr>
</tbody>
</table>

Valerio Schreiber, Denton, Coghillan, submitted 2012
Due to the lack of robust data allowing to define adequately an abnormal response of pulmonary circulation at exercise, PAP and or PVR criteria to define PH on exercise should not be reintroduced at the present time in the definition of PH.

Further studies are needed to define which values of PAPm and PVR on exercise could be considered as abnormal predicting subsequently the occurrence of an overt PH and leading to some therapeutic implications.

A first step should be to define a standardized protocol of exercise for evaluation of hemodynamic on exercise.
• C. Are there novel drugs and toxins inducing PAH?

- Benfluorex
- Dasatinib
- Interferon
- Methylphenidate
Fenfluramine-like cardiovascular side-effects of benfluorex


<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
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<tr>
<td>mPAP mmHg</td>
<td>51</td>
<td>40</td>
<td>60</td>
<td>45</td>
<td>28</td>
</tr>
<tr>
<td>Cl L·min⁻¹·m⁻²</td>
<td>1.37</td>
<td>2.3</td>
<td>3.2</td>
<td>3.3</td>
<td>2.42</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>9</td>
<td>3</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>wedged pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute vasoreactivity#</td>
<td>Neg.</td>
<td>Pos.</td>
<td>Neg.</td>
<td>Neg.</td>
<td>NA</td>
</tr>
<tr>
<td>6MWD m</td>
<td>265</td>
<td>363</td>
<td>295⁺</td>
<td>132⁺</td>
<td>218</td>
</tr>
</tbody>
</table>

1 case of valvular heart disease
Pulmonary hypertension associated with benfluorex exposure

Laurent Savale1,2,3, Marie-Camille Chaumais1,3,4, Vincent Cottin5, Emmanuel Bergof6, Irène Frachon7, Grégoire Prevot8, Christophe Pison9, Claire Dromer10, Patrice Poubeau11, Nicolas Lamblin12, Gilbert Habib13, Martine Reynaud-Gaubert14, Arnaud Bourdin15, Olivier Sanchez16, Pascale Tubert-Bitter17,18, Xavier Jais1,2,3, David Montani1,2,3, Olivier Sitbon1,2,3, Gérard Simonneau1,2,3 and Marc Humbert1,2,3

Eur Respir J. 2012 Apr 20. [Epub ahead of print]

Figure 1. Number of newly-diagnosed benfluorex-associated PH patients per year between 1999 and March 2011.

Figure 2. Type of benfluorex-associated pulmonary hypertension identified between 1999 and March 2011.

- Pulmonary hypertension (mPAP ≥ 25 mmHg) n=85
  - Post-capillary pulmonary hypertension (Pcwp > 15 mmHg; TPG ≤ 12 mmHg) n=2
  - Pre-capillary pulmonary arterial hypertension (Pcwp > 15 mmHg) n=70
  - Mixed pre- and post-capillary hypertension (Pcwp > 15 mmHg; TPG > 12 mmHg) n=13
<table>
<thead>
<tr>
<th></th>
<th>Benfluorex</th>
<th>Dexfenfluramine &amp; Fenfluramine</th>
<th>(P^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n</td>
<td>70</td>
<td>109</td>
<td></td>
</tr>
<tr>
<td>Age, years (median [IQR])</td>
<td>61 [51-71]</td>
<td>52 [44-59]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender (Female:Male) ratio</td>
<td>3.1</td>
<td>19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2) (median [IQR])</td>
<td>30 (26-34)</td>
<td>27 (24-33)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Delay between first anorexigen exposure and PAH diagnosis, months (median [IQR])</td>
<td>108 [60-144]</td>
<td>78 [43-140]</td>
<td>NS</td>
</tr>
<tr>
<td>Anorexigen exposure duration, months (median [IQR])</td>
<td>30 [12-70]</td>
<td>6 [3-12]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA-FC, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>12 (17%)</td>
<td>15 (14%)</td>
<td>NS</td>
</tr>
<tr>
<td>III</td>
<td>52 (74%)</td>
<td>71 (65%)</td>
<td>NS</td>
</tr>
<tr>
<td>IV</td>
<td>6 (9%)</td>
<td>23 (21%)</td>
<td></td>
</tr>
<tr>
<td>6MWD, m (median [IQR])</td>
<td>319 [209-372]</td>
<td>250 [121-355]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hemodynamics (mean±SD):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAP, mmHg</td>
<td>9±5</td>
<td>11±6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>47±11</td>
<td>60±12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pswp, mmHg</td>
<td>10±4</td>
<td>9±3</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index, L/min/m(^2)</td>
<td>2.4±0.6</td>
<td>2.2±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>PVRi, mmHg /L/min/m(^2)</td>
<td>17±8</td>
<td>26±11</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

L Savale et al Eur Respir J, 2012 Apr 20. [Epub ahead of print]
TYROSINE KINASE INHIBITORS

Tyrosine kinase inhibitors

- Imatinib
  - PDGFR
  - c-kit
  - Bcr-Abl
- Dasatinib
  - PDGFR
  - c-kit
  - Bcr-Abl
  - Src

Multikinase inhibitors

- Sorafenib
  - PDGFR
  - c-kit
  - Bcr-Abl
  - VEGFR
  - Raf-1
- Sunitinib
  - PDGFR
  - VEGFR
  - c-kit
  - FLT3
  - RET
Pulmonary Arterial Hypertension in Patients Treated by Dasatinib

David Montani, MD, PhD; Emmanuel Bergot, MD; Sven Günther, MD; Laurent Savale, MD, PhD; Anne Bergeron, MD, PhD; Arnaud Bourdin, MD, PhD; Helene Bouvaist, MD; Matthieu Canuet, MD; Christophe Pison, MD, PhD; Margareth Macro, MD; Pascal Poubeau, MD; Barbara Girerd; Delphine Natali, MD; Christophe Guignabert, PhD; Frédéric Perros, PhD; Dermot S. O’Callaghan, MD; Xavier Jaïs, MD; Pascale Tubert-Bitter, PhD; Gerard Zalcman, MD, PhD; Olivier Sitbon, MD, PhD; Gérald Simonneau, MD; Marc Humbert, MD, PhD

Background.—The French pulmonary hypertension (PH) registry allows the survey of epidemiological trends. Isolated cases of precapillary PH have been reported in patients who have chronic myelogenous leukemia treated with the tyrosine kinase inhibitor dasatinib.

Methods and Results.—To describe incident cases of dasatinib-associated PH reported in the French PH registry. From the approval of dasatinib (November 2006) to September 30, 2010, 9 incident cases treated by dasatinib at the time of PH diagnosis were identified. At diagnosis, patients had moderate to severe precapillary PH with functional and hemodynamic impairment. No other incident PH cases were exposed to other tyrosine kinase inhibitors at the time of PH diagnosis. Clinical, functional, or hemodynamic improvements were observed within 4 months of dasatinib discontinuation in all but 1 patient. Three patients required PH treatment with endothelin receptor antagonist (n=2) or calcium channel blocker (n=1). After a median follow-up of 9 months (min-max 3–36), the majority of patients did not demonstrate complete clinical and hemodynamic recovery, and no patients reached a normal value of mean pulmonary artery pressure (≤20 mm Hg). Two patients (22%) died at follow-up (1 of unexplained sudden death and 1 of cardiac failure in the context of septicemia, respectively, 8 and 12 months after dasatinib withdrawal). The lowest estimate of incident PH occurring in patients exposed to dasatinib in France was 0.45%.

Conclusions.—Dasatinib may induce severe precapillary PH, suggesting a direct and specific effect of dasatinib on pulmonary vessels. Improvement is usually observed after withdrawal of dasatinib. (Circulation. 2012;125:00-00.)
10. Pulmonary hypertension and the link with IFN signalling

we have found that as with type II IFN-γ, type I IFN-α and IFN-β activate pulmonary vascular cells to release ET-1 and that both pegylated and non-pegylated forms of IFN-α activate human pulmonary artery smooth muscle cells (Badger et al., 2011). We have also demonstrated that direct stimulation of pulmonary artery smooth muscle cells with virus and viral toll like receptor ligands results in activation with IP10 and ET-1 release (Badiger, De Sousa, Wort, Paul-Clark, & Mitchell, 2008; Badger et al., 2008). This all adds more weight to the growing body of evidence that viruses and/or IFN may be implicated in the development of pulmonary hypertension.
Sildenafil therapy for interferon-β-1a-induced pulmonary arterial hypertension: a case report.

Irreversible pulmonary hypertension associated with the use of interferon alpha for chronic hepatitis C.

Today about 10 cases reported in the French registry
Methylphenydate and Pulmonary Hypertension

• Methylphenydate is a drug used in children against hyperactivity disorder
• Inhibiting reuptake of Dopamine and Norepinephrine
• Amphetamine- like effects is also suspected

Pulmonary Arterial Hypertension in an adolescent treated with Methylphenidate  Karaman LG et al J Child Adolesc Psychopharmacol. 2010 Jun;20(3):229-31
• D. Which changes in group 5?
  - Should we maintain sickle cell disease PAH in group 1?
  - New subgroups groups identified or previous one to shift to another PH group?
Clinical Classification of Pulmonary Hypertension


1 Pulmonary arterial hypertension (PAH)
   1.1 Idiopathic
   1.2 Heritable
      1.2.1 BMPR2
      1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
      1.2.3 Unknown
   1.3 Drugs and toxins induced
   1.4 Associated with (APAH)
      1.4.1 Connective tissue diseases
      1.4.2 HIV infection
      1.4.3 Portal hypertension
      1.4.4 Congenital heart disease
      1.4.5 Schistosomiasis
      1.4.6 Chronic haemolytic anaemia
   1.5 Persistent pulmonary hypertension of the newborn

1' Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

2 Pulmonary hypertension due to left heart disease
   2.1 Systolic dysfunction
   2.2 Diastolic dysfunction
   2.3 Valvular disease

3 Pulmonary hypertension due to lung diseases and/or hypoxia
   3.1 Chronic obstructive pulmonary disease
   3.2 Interstitial lung disease
   3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   3.4 Sleep-disordered breathing
   3.5 Alveolar hypoventilation disorders
   3.6 Chronic exposure to high altitude
   3.7 Developmental abnormalities

4 Chronic thromboembolic pulmonary hypertension

5 PH with unclear and/or multifactorial mechanisms
   5.1 Haematological disorders: myeloproliferative disorders, splenectomy.
   5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis
A Hemodynamic Study of Pulmonary Hypertension in Sickle Cell Disease

Florence Parent, M.D., Dora Bachir, M.D., Jocelyn Inamo, M.D., François Lionnet, M.D., Françoise Driss, M.D., Gylna Loko, M.D., Anoosh Habibi, M.D., Soumya Bennani, M.D., Laurent Savale, M.D., Serge Adnot, M.D., Bernard Maitre, M.D., Azzedine Yaïci, M.D., Leila Hajji, M.D., Dermot S. O’Callaghan, M.D., Pierre Clerson, M.D., Robert Girot, M.D., Frederic Galacteros, M.D., and Gerald Simonneau, M.D.

New Engl J Med 2011

445 Patients were assessed for eligibility

42 Were excluded
- 29 had severe renal insufficiency
- 8 had severe lung disease
- 5 had severe liver disease

403 Signed informed consent

5 Were excluded owing to unstable clinical condition

398 Underwent Doppler echocardiographic screening

289 (73%) Had TRJV ≤ 2.3 m/sec

Group 1
289 Did not have pulmonary hypertension

109 (27%) Had TRJV ≥ 2.3 m/sec

109 Were suspected of having pulmonary hypertension

13 Declined to undergo right heart catheterization

96 Underwent right heart catheterization

Group 2
72 Were confirmed not to have pulmonary hypertension (mean PA pressure, ≤ 25 mm Hg)

11 Had precapillary pulmonary hypertension (PCWP, ≤ 15 mm Hg)

Group 3
24 Were confirmed to have pulmonary hypertension (mean PA pressure, ≥ 25 mm Hg)

13 Had postcapillary pulmonary hypertension (PCWP, > 15 mm Hg)
<table>
<thead>
<tr>
<th>No of Patients (Percentage)</th>
<th>Pre-capillary PAH</th>
<th>Post-capillary PH</th>
<th>No PH on RHC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11 (2.9%)</td>
<td>13 (3.3%)</td>
<td>72 (18.7%)</td>
</tr>
<tr>
<td>mPAP (mm Hg)</td>
<td>28±4</td>
<td>32±7</td>
<td>19±3</td>
</tr>
<tr>
<td>sPAP (mm Hg)</td>
<td>43±7</td>
<td>45±8</td>
<td>28±4</td>
</tr>
<tr>
<td>dPAP (mm Hg)</td>
<td>15±5</td>
<td>22±6</td>
<td>12±3</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>5±2</td>
<td>13±5</td>
<td>7±2</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>10±3</td>
<td>21±5</td>
<td>11±3</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>8.2±1.6</td>
<td>9.1±2.1</td>
<td>8.4±2.1</td>
</tr>
<tr>
<td>PVR (dyn.s.cm⁻⁵)</td>
<td>178±55</td>
<td>104±26</td>
<td>72±26</td>
</tr>
</tbody>
</table>

New Engl J Med 2011
## Hemodynamics at Diagnosis in different PAH subgroups

<table>
<thead>
<tr>
<th>PAH subgroups</th>
<th>IPAH* (n=288)</th>
<th>CTD-PAH* (n=157)</th>
<th>PoPH* (n=127)</th>
<th>CHD-PAH* (n=35)</th>
<th>HIV-PAH** (n=59)</th>
<th>Precap-PH in SCD*** (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP, mmHg</td>
<td>8 ± 5</td>
<td>7 ± 5</td>
<td>8 ± 6</td>
<td>7 ± 5</td>
<td>8 ± 5</td>
<td>5 ± 2</td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>49 ± 13</td>
<td>41 ± 9</td>
<td>47 ± 12</td>
<td>51 ± 16</td>
<td>49 ± 10</td>
<td>28 ± 4</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>9 ± 4</td>
<td>8 ± 4</td>
<td>9 ± 4</td>
<td>8 ± 4</td>
<td>9 ± 5</td>
<td>10 ± 3</td>
</tr>
<tr>
<td>Cardiac Index, L/min/m²</td>
<td>2.4 ± 0.8</td>
<td>2.8 ± 0.9</td>
<td>3.0 ± 1.0</td>
<td>3.0 ± 1.0</td>
<td>2.9 ± 0.7</td>
<td>5.8 ± 1.3</td>
</tr>
<tr>
<td>PVR, dyn.sec.cm⁻⁵</td>
<td>831 ± 461</td>
<td>649 ± 379</td>
<td>611 ± 311</td>
<td>753 ± 370</td>
<td>737 ± 328</td>
<td>178 ± 55</td>
</tr>
</tbody>
</table>

EDITORIAL

Pulmonary hypertension in patients with sickle cell disease: not so frequent but so different. The importance of right heart catheterisation

G. Simonneau and F. Parent

Finally, pre-capillary PH associated with sickle cell disease appears quite different from the other forms of PAH in terms of both its haemodynamic profile and response to specific PAH therapies. These observations call into question the rationale for keeping sickle cell disease in group 1 (PAH) of the clinical PH classification system.
• Although limited, autopsy studies also provide insight into the presence of pulmonary vascular disease in patients with sickle cell disease.

• In a series of 20 patients with sickle hemoglobinopathy, the pulmonary vascular bed of all 20 patients revealed changes considered diagnostic of pulmonary hypertension, ranging from grade I to grade IV. Reversible hypertensive changes (grade I to grade III) were seen in 8 patients, and irreversible changes (grade IV lesions) were seen in the remaining 12 patients. Plexiform lesions were seen in 12/20 patients. 

• In another series of 21 patients who experienced sudden/unexpected death during a hospital admission for an acute illness (vasooclusive crisis n=13, sepsis/infection = 5, acute kidney injury n=2, CNS hemorrhage n=1), 7 patients demonstrated grades I–IV lesions with one reported case with plexiform lesions.


1. **Pulmonary arterial hypertension (PAH)**
   1.1 Idiopathic
   1.2 Heritable
      1.2.1 BMPR2
      1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
      1.2.3 Unknown
   1.3 Drugs and toxins induced
   1.4 Associated with (APAH)
      1.4.1 Connective tissue diseases
      1.4.2 HIV infection
      1.4.3 Portal hypertension
      1.4.4 Congenital heart disease
      1.4.5 Schistosomiasis
      1.4.6 **Chronic haemolytic anaemia**
   1.5 Persistent pulmonary hypertension of the newborn

1’ **Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis**

2. **Pulmonary hypertension due to left heart disease**
   2.1 Systolic dysfunction
   2.2 Diastolic dysfunction
   2.3 Valvular disease

3. **Pulmonary hypertension due to lung diseases and/or hypoxia**
   3.1 Chronic obstructive pulmonary disease
   3.2 Interstitial lung disease
   3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   3.4 Sleep-disordered breathing
   3.5 Alveolar hypoventilation disorders
   3.6 Chronic exposure to high altitude
   3.7 Developmental abnormalities

4. **Chronic thromboembolic pulmonary hypertension**

5. **PH with unclear and/or multifactorial mechanisms**
   5.1 Haematological disorders: myeloproliferative disorders, splenectomy.
   5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis
Survey of PAH specific therapy in Group 5 (Ivan Robbins)

What patients in WHO Group 5 have you treated with PAH specific therapy?

- Sarcoidosis: 28
- End-stage renal disease on hemodialysis: 11
- Pulmonary vasculitis: 19
- Fibrosing mediastinitis: 5
- Gaucher disease: 4
- Hematologic disorders: 9
- Other: 4

Other conditions may be included in the "Other" category.
5th World Symposium on Pulmonary Hypertension

Nice Acropolis, Nice
February 27-28 / March 1, 2013