Epidemiology, Physiology and Evaluation of Eisenmenger Syndrome

Kwangju Christian Hospital
Kim Yong Wook
Eisenmenger syndrome

Victor Eisenmenger initially described the clinical features of a patient with PAH and a right to left shunt in 1897. A 32-year-old man.

The term Eisenmenger syndrome (ES), coined by Paul Wood in 1958, embodies PAH which is consequence of a systemic to pulmonary arterial connection.

Victor Eisenmenger 1864~1932
Epidemiology of Eisenmenger Syndrome
1. PAH: Pulmonary Arterial Hypertension
   1.1 Idiopathic PAH
   1.2 Heritable PAH
   1.3 Drug and toxin induced
   1.4 Associated with
      1.4.1 Connective tissue diseases
      1.4.2 HIV infection
      1.4.3 Portal hypertension
      1.4.4 Congenital heart diseases
      1.4.5 Schistosomiasis
      1.4.6 Chronic hemolytic anemia
   1.5 PPHN
   1` PVOD and/or PCH
2. PH owing to left-sided heart disease
3. PH owing to lung diseases and/or hypoxia
4. CTEPH; chronic thromboembolic pulmonary hypertension
5. PH with unclear multifactorial mechanisms
Pulmonary hypertension (PH) affects > 25 million individuals worldwide and causes premature disability and death for many. The diagnosis and treatment of PH have advanced dramatically through the development of a clearly defined diagnostic classification, an evidence-based treatment algorithm for adults with pulmonary arterial hypertension using life-saving medications, and life-saving surgical procedures. However, worldwide education and training of physicians has lagged behind advances in the management of PH. Expertise in the diagnosis and management of PH is uncommon, even though physicians receive training on PH during their graduate and postgraduate education. Advances in worldwide physician education and training in PH will require substantial organization and work. Organizations working in this field will need to work collaboratively to maximize funding for education and to optimize the achievement of educational goals. Political, economic, and cultural barriers must be identified and overcome as part of any strategic plan. Global education should include training objectives for generalist, non-PH specialist, and PH specialist physicians.

*CHEST 2010; 137(6)(Suppl):85S–94S*

**Abbreviations:** CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension

**Pulmonary hypertension (PH) affects > 25 million individuals worldwide**
Korean PAH Registry of PHT (2011)

<table>
<thead>
<tr>
<th>Classification</th>
<th>case</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic (IPAH)</td>
<td>225</td>
<td>22.2</td>
</tr>
<tr>
<td>Congenital systemic to pulmonary shunts</td>
<td>243</td>
<td>24.0</td>
</tr>
<tr>
<td>Chronic thrombo-embolic disease</td>
<td>500</td>
<td>49.3</td>
</tr>
<tr>
<td>Familial</td>
<td>15</td>
<td>1.5</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>31</td>
<td>3.1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1014</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

Prevalence of PAH : 20.2/million

Jo Won Jung. Ajou University School of Medicine.
GUCH patients in Samsung Medical Center

<table>
<thead>
<tr>
<th></th>
<th>Seoul SMC 2007 (n=256)</th>
<th>%</th>
<th>Seoul SMC 2007 (n=256)</th>
<th>%</th>
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<tbody>
<tr>
<td>1</td>
<td>ASD</td>
<td>36.8</td>
<td>Pulmonary stenosis</td>
<td>2.3</td>
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<tr>
<td>2</td>
<td>VSD</td>
<td>17.0</td>
<td>AVSD</td>
<td>1.9</td>
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<tr>
<td>3</td>
<td>TOF</td>
<td>14.0</td>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>PDA</td>
<td>7.0</td>
<td>Eisenmenger syn.</td>
<td>7.0</td>
</tr>
<tr>
<td>5</td>
<td>Pulmonary atresia</td>
<td>4.6</td>
<td>Marfan syndrome</td>
<td>5.8</td>
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<tr>
<td>6</td>
<td>TGA</td>
<td>3.5</td>
<td>Coronary AV fistular</td>
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<td>7</td>
<td>Ebstein`s anomaly</td>
<td>2.7</td>
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### Epidemiology of the Pulmonary Arterial hypertension (PAH)

<table>
<thead>
<tr>
<th>Nation</th>
<th>Age</th>
<th>No. of patients</th>
<th>Incidence of PAH</th>
<th>Prevalence of PAH</th>
<th>% of CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>children</td>
<td>50</td>
<td>3.7/million</td>
<td>24.0%</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>&gt;18years</td>
<td>674</td>
<td>2.4/mill./Y</td>
<td>15.0/million</td>
<td>11.3%</td>
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<tr>
<td>Korea</td>
<td>all</td>
<td>1014</td>
<td>20.2/million</td>
<td>24.0%</td>
<td></td>
</tr>
<tr>
<td>Scotland</td>
<td>adult</td>
<td>374</td>
<td>7.6/mill./Y</td>
<td>26.0/million</td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>children</td>
<td>63</td>
<td></td>
<td></td>
<td>37.0%</td>
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</table>
Epidemiology of the Eisenmenger Syndrome (ES) in patients with CHD

<table>
<thead>
<tr>
<th>Nation</th>
<th>Age</th>
<th>No. of patients</th>
<th>% of PAH with CHD</th>
<th>% of ES with CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutch</td>
<td>&gt;18 years</td>
<td>5970 CHD</td>
<td>4.2%</td>
<td>2.4%</td>
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<tr>
<td>Samsung H.</td>
<td>adult</td>
<td>256 CHD</td>
<td></td>
<td>7%</td>
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<tr>
<td>Paul Wood</td>
<td></td>
<td>727 CHD</td>
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<td>17.5%</td>
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<tr>
<td>Belgium</td>
<td>&gt;18 years</td>
<td>91 ES</td>
<td></td>
<td>11/million</td>
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<tr>
<td>Western countries</td>
<td>adult</td>
<td></td>
<td></td>
<td>1.6~12.5/million</td>
</tr>
</tbody>
</table>

25-50% of PAH affected by ES
The incidence of CHD at 8 to 12 per 1,000 live births.

Worldwide, about 600,000 babies are born annually with significant CHD, 50% or more will die of infection and heart failure in infancy.

Globally, 80% of the population lives outside the developed countries.

Only 2% to 15% of patients receive curative intervention.

We calculate that there are approximately 3.2 million children worldwide with an isolated ASD, VSD, or PDA who if untreated and surviving infancy would develop pulmonary vascular disease.

Approximately 30% of children with CHD who do not undergo surgical repair will develop pulmonary vascular disease.
Advances in pediatric cardiology/cardiac surgery

1. Increased the number of patients with CHD surviving into adulthood.
2. Decreased the number of patients overall with Eisenmenger syn.

<table>
<thead>
<tr>
<th>Period</th>
<th>Description</th>
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<tr>
<td>1940~1960</td>
<td>Open heart surgery was confined mainly to some patients with PDA, ASD, PS.</td>
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<tr>
<td>1960~1980</td>
<td>The results of open heart surgery were not particularly good except in a few centers.</td>
</tr>
<tr>
<td>1980~2000</td>
<td>Surgical repair of most defects reached high standards and high volume, although for complex lesions the techniques underwent continuous modification</td>
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<tr>
<td>2000~2011</td>
<td>Surgical repair and catheter intervention</td>
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</table>

<table>
<thead>
<tr>
<th>Seoul SMC</th>
<th>1996(n=514)</th>
<th>2007(n=256)</th>
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<tbody>
<tr>
<td>Natural survivors</td>
<td>81%</td>
<td>35%</td>
</tr>
<tr>
<td>Postoperative survivors</td>
<td>19%</td>
<td>65%</td>
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</table>
Physiology
of
Eisenmenger syndrome
The physiology of Pulmonary circulation

Pulmonary vascular resistance (PVR) is determined by:

1. The cross sectional area of small muscular arteries and arterioles
2. Blood viscosity
3. Total mass of the lung
4. Stenosis of the blood vessels
5. Extramural compression of the blood vessels

Normal PVR is 1 Wood unit (or 67±23 dyne.sec/cm) which 1/10 of SVR
A key factor is balanced release of Nitric oxide and Endothelin by endothelial cell.
Response of the PA to Increased Blood Flow
Clinical classification of congenital, systemic-to-pulmonary shunts associated with PAH.

- **ESC/ERS GUIDELINES**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
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<tbody>
<tr>
<td>A. Eisenmenger’s syndrome</td>
<td></td>
</tr>
<tr>
<td>B. PAH associated with systemic-to-pulmonary shunts</td>
<td></td>
</tr>
<tr>
<td>C. PAH with small defects: similar to idiopathic PAH</td>
<td></td>
</tr>
<tr>
<td>D. PAH after corrective cardiac surgery</td>
<td></td>
</tr>
</tbody>
</table>

ESC/ERS GUIDELINES. Eur Respir J 2009; 34: 1219–1263
Hyperkinetic PHT is associated with large left to right shunt lesions.

- Large left to right shunt
- An increase in PBF
- A direct transmission of the systemic pressure to the PA
- Compensatory pulmonary vasoconstriction
  - Increased expression of numerous mediators and receptors
  - Increased expression of signaling molecules
  - Increase in PVR

Hyperkinetic PH is usually reversible if the cause is eliminated before permanent change occurs in the pulmonary arteries.
Pathologic change: the pathogenesis of chronic PAH

1. Endothelial dysfunction and vasoconstriction

2. Vascular remodeling:
   Proliferation of smooth muscle or epithelial cell

3. In situ thrombosis

Elevated PA pressure: 3 well characterized vascular change

The pathogenesis of chronic PAH

1. Risk factors and associated conditions:
   - Collagen vascular disease
   - Congenital heart disease
   - Portal hypertension
   - HIV infection
   - Drugs and toxins
   - Pregnancy

2. Vascular injury:
   - Endothelial dysfunction
     - Reduced nitric oxide synthase
     - Reduced prostacyclin production
     - Increased thromboxane production
     - Increased endothelin 1 production
   - Vascular smooth muscle dysfunction
     - Impaired voltage-gated potassium channel (K_v1.5)

3. Disease progression:
   - Loss of response to short-acting vasodilator trial
   - Smooth muscle hypertrophy
   - Adventitial and intimal proliferation
   - In situ thrombosis
   - Plexiform lesion
   - Advanced vascular lesion

Pathogenesis of pulmonary arterial hypertension.
(From Gaine S. Pulmonary hypertension. JAMA 2000;284(24):3160–8;
The 3 main therapeutic pathways currently emphasized in the treatment of PAH.
Response of the RV to Increased Afterload
Response of the RV to Increased Afterload

Important determinants of the response of the RV to increased afterload.

1. The contractile performance of the cardiomyocyte
2. The rate and magnitude of the increase in RV afterload
3. The time of onset of disease
The rate and magnitude of the increase in RV afterload

1. If pulmonary hypertension develops abruptly.
   - acute right-sided heart failure
   - thin RV cannot sustain sudden pressure loads over 40 to 50 mmHg.

2. If pulmonary hypertension develops slowly.
   - the RV hypertrophies
   - and it can tolerate mild PH without produce clinical problem.
     (a compensatory increase in muscle mass)

RV adaptation also depends on the rapidity and magnitude at which the increase in afterload occurs.
1. If pulmonary hypertension develops abruptly, acute right-sided heart failure can occur. Thin RV cannot sustain sudden pressure loads over 40 to 50 mmHg.

- **RV pressure overload**
  - increase in end-systolic volume
  - a decrease in ejection fraction

- **Reduced cardiac output**

- **Systemic hypotension**

- **Reduced RV tissue perfusion**
  - decreased RV coronary perfusion

- **RV free wall ischemia**

- **Reduced RV free wall contractility**

The rate of the increase in RV afterload: **abruptly**
The rate of the increase in RV afterload: **slowly**

2. If pulmonary hypertension develops slowly, the RV hypertrophies and it can tolerate mild PH without produce clinical problem.

- Left to right shunt
- Increased pulmonary blood flow
- Endothelial dysfunction and vascular remodeling
- Increase in PVR
- RV hypertrophy

The time of onset of disease is important.

At birth, the ventricles have similar muscle masses as the work required of the ventricles in utero is approximately equal.

After birth, PVR decreases, SVR increases. LV hypertrophic growth outpaces that for the RV.

If the RV is continuously exposed to systemic pressure, its growth and function parallel those for the LV.

The time of onset of disease

Patients with ES and a defect distal to the TV

1. Regression of RV wall thickness does not occur
   fetal morphology persists throughout infancy, adolescence, and adulthood.
2. RV and LV wall thickness are equal
   independent of age, defect type, PVR, magnitude of shunt flow.

=> Preservation of biventricular function

Preservation of biventricular function
is likely the primary reason patients with ES fare so much better than other adults with severe pulmonary hypertension.
Severe PH without RV failure.

William E. Hopkins Am J Cardiol 2002;89:34–38

FIGURE 3. Wall thickness. Linear regression analysis of the relation between right and left ventricular wall thickness in fetuses with normal hearts, infants with nonrestrictive VSD and left-to-right shunt (pre-Eisenmenger phase), and adolescents and adults with nonrestrictive post-tricuspid defects and Eisenmenger syndrome.
Pathophysiology of Eisenmenger syndrome

- Left to right shunt
- Increased pulmonary blood flow
- Mechanical stretching in the pulmonary vasculature
- Endothelial dysfunction and Vascular remodeling
- Produces the progressive structural & histologic changes
- Increase in PVR
- RV hypertrophy
- Inverted shunt (Right to left)

Increased expression of numerous mediators and receptors
- Increased expression of signaling molecules
  1. Endothelin-1
  2. NO
  3. Prostacyclin
  4. Thromboxan A2

Risk factors for pulmonary hypertension in CHD

1. The size of the shunt and subsequent blood flow
   - Small-to-moderate size VSD: only 3%
   - Larger size VSD (greater than 1.5 cm in diameter): 50%

2. The type of defect
   - Nearly all patients with Truncus arteriosus
   - Approximately 50% of patients with large VSD
   - Only 10% of patients with ASD

Comparison of the hemodynamics and survival of adult with severe primary pulmonary hypertension or Eisenmenger syndrome


<table>
<thead>
<tr>
<th>survival</th>
<th>at 1 year</th>
<th>at 2 years</th>
<th>at 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eisenmenger Syndrome</td>
<td>97%</td>
<td>89%</td>
<td>77%</td>
</tr>
<tr>
<td>Primary PH</td>
<td>77%</td>
<td>69%</td>
<td>35%</td>
</tr>
</tbody>
</table>

1. The progression of the pulmonary vasculopathy is slower.
   Preservation of RV wall thickness prevented progressive RV failure in the face of high PA pressures.

2. The second protective mechanism may be the defect itself.
   Unloads RV, and preserves LV cardiac output.
   This effect may be particularly important during exercise to protect RV from a sudden increase in pulmonary vascular pressure that would be expected to occur with an increase in blood flow.
Evaluation of
Eisenmenger Syndrome
Evaluation of Eisenmenger Syndrome

1. History taking and Symptoms
2. Physical examinations
3. Chest X-ray
4. ECG
5. Echocardiography
6. Cardiac catheterization
7. Lung biopsy
### The symptoms associated with PAH and ES

<table>
<thead>
<tr>
<th>Clinical presentations in PAH</th>
<th>Clinical presentations in ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dyspnea (with exertion)</td>
<td>1. Hemoptysis</td>
</tr>
<tr>
<td>2. Fatigue</td>
<td>2. CVA</td>
</tr>
<tr>
<td>3. Syncope</td>
<td>3. Hemorrhage</td>
</tr>
<tr>
<td>5. Near syncope</td>
<td>5. Secondary erythrocytosis</td>
</tr>
<tr>
<td>7. Leg edema</td>
<td>7. Cardiac arrhythmia</td>
</tr>
</tbody>
</table>

1. Cyanosis with or without clubbing
2. Distended neck vein
3. A single S2, or it splits narrowly. Loud P2
4. A diastolic murmur of PR
5. A holosystolic murmur of TR
6. Signs of right-sided heart failure: hepatomegaly, ankle edema
7. Arrhythmia

### WHO PH functional assessment classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>Class II</td>
<td>Slight limitation of physical activity; ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>Class III</td>
<td>Marked limitation of physical activity; comfortable at rest, but less-than-ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope; signs of right-sided heart failure may be present.</td>
</tr>
<tr>
<td>Class IV</td>
<td>Inability to carry out any physical activity without symptoms; dyspnea and/or fatigue may even be present at rest; discomfort is increased by any physical activity; signs of right-sided heart failure are usually present.</td>
</tr>
</tbody>
</table>
Chest radiography

1. Peripheral hypovascularity: attenuated peripheral vascular markings
2. Enlarged main and hilar pulmonary artery shadows
3. RV enlargement:
   obscuration of the retrosternal clear space on a lateral view
Electrocardiography

Right ventricular hypertrophy
Right-axis deviation
The absence of these findings does not exclude PAH
1. To evaluate cardiac anatomy

2. The estimation of PA pressure:
   is based on the peak velocity of the jet of TR.

3. Other echocardiographic variables
   that might reinforce suspicion of PH include:
   1) an increased velocity of PR
   2) short acceleration time of RV ejection into the PA
   3) increased dimensions of RV and RA
   4) abnormal shape and function of the interventricular septum
   5) increased RV wall thickness
   6) dilatation of the MPA

Systolic Pulmonary Artery Pressure.

sPAP = RV systolic pressure in the absence of PV stenosis or outflow tract obstruction.

RV systolic pressure

= RA pressure (RAP) + pressure gradient between RV & RA.

= RAP + 4(TRv)^2

The modified Bernoulli equation: \( \Delta P = 4 \times V^2 \)

V is the tricuspid regurgitant velocity (TRv).

Echocardiographic Indexes for the Non-Invasive Evaluation of Pulmonary Hemodynamics.
In a recent study, in 48% of 63 patients studied, echocardiography-derived sPAP differed more than 10 mmHg from invasively measured sPAP; underestimation or overestimation. due to such factors
1. Inaccuracy of predicted RAP
2. Inaccuracy of angle of interrogation
3. Incomplete signal envelope of regurgitant flow

To minimize error
1. TRv should be measured in multiple views: seeking the maximal TRv.
2. The use of color flow Doppler: to obtain the best alignment
Cardiac catheterization

Right-heart catheterization is the standard for PAH diagnosis.

1. Hemodynamic measurements
   - Oxygen saturation (IVC, SVC, RV, PA)
   - Pressure (RA, RV, PA, PCWP)
   - Cardiac output/ index
   - Pulmonary vascular resistance

2. Vasodilator testing should be done in all cases of PAH.

3. Angiography:
   - to avoid precipitating a pulmonary hypertensive crisis

In pediatric patients, two studies have found that major complications including arrhythmia, pulmonary hypertensive crisis, and cardiac arrest were 5% and 6%. Mary P. Mullen, MD, Pediatr Crit Care Med 2010 Vol. 11, No. 2
Cardiac catheterization: Pulmonary vascular resistance

Pulmonary vascular resistance (PVR)

\[ PVR = \frac{\text{mean PA pressure} - \text{mean LA pressure}}{\text{pulmonary blood flow (Qp)}} \]

Patients were inoperable

if the PVR calculation exceeded 8 Wood’s Units,

particularly if resistance did not fall with oxygen administration or

if the PVR/SVR ratio was greater than 0.5.
Cardiac catheterization: Vasodilator testing

Pulmonary vasoreactivity test:

- iNO, iv Epoprostenol, iv Adenosine, Oxygen,
  - Epoprostenol: 2-12 ng/kg per min.
  - iNO: 20-40 ppm for 5 min.
  - iv Adenosine: 50-350 ug/kg/minute

A positive response to the vasodilator test:

- decrease ≥ 10 mmHg in the mean PAP
- a mean PAP ≤ 40mmHg
- an unchanged or increased cardiac output
The 6-minute walk test (6 MWT)

The 6-MWT is technically simple, inexpensive, reproducible. The best test to classify the severity of PAH and estimate prognosis.

Correlates well with cardiopulmonary exercise testing (CPET) measures and should be used to assess exercise capacity at diagnosis as well as serially with treatment of the patient who has PAH.

Fig. 6. Bosentan Trial: change in 6-minute walking distance from baseline to week 20.

Considerations before Initiating Therapy in ES

Evaluation of severity

1. Clinical (WHO-FC)
2. Echocardiographic parameters
3. Hemodynamic parameters on right heart catheterization
4. Exercise capacity (6MWT, cardiopulmonary exercise test)
5. Biochemical markers (NT-pro BNP)

6. Lung biopsy
   is not recommended because it has considerable risks
   a very low likelihood of altering the diagnosis or treatment.
Korean PAH Registry of PHT (2011)

Age distribution
## Korean PAH Registry of PHT (2011)

### Diagnostic Classification

<table>
<thead>
<tr>
<th></th>
<th>CHD</th>
<th>CTD</th>
<th>Familial</th>
<th>IPAH</th>
<th>others</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Cardio</td>
<td>102</td>
<td>54</td>
<td>2</td>
<td>55</td>
<td>19</td>
<td>232</td>
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<tr>
<td>Ped cardio</td>
<td>134</td>
<td></td>
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<td></td>
<td>8</td>
<td>176</td>
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<tr>
<td>Pulmo</td>
<td>7</td>
<td>41</td>
<td>13</td>
<td>136</td>
<td>3</td>
<td>200</td>
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<td>Rheuma</td>
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<td>405</td>
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<td>406</td>
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<td><strong>Total</strong></td>
<td>243</td>
<td>500</td>
<td>15</td>
<td>225</td>
<td>31</td>
<td>1014</td>
</tr>
<tr>
<td></td>
<td>Event Description</td>
<td>Location</td>
<td>Year</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>The first World symposium on PH</td>
<td>Geneva, Switzerland</td>
<td>1973</td>
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<td></td>
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</tr>
<tr>
<td>2</td>
<td>The second World symposium on PH</td>
<td>Evian, France</td>
<td>1998</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>The Third World Symposium on PAH</td>
<td>Venice, Italy</td>
<td>2003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>The 4th World Symposium on PH</td>
<td>Dana Point, California</td>
<td>2008</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ESC/ERS guidelines: arbitrary criteria for estimating the presence of PH based on TR peak velocity and Doppler-calculated systolic PA pressure (Ppa) at rest (assuming a normal RA pressure of 5 mmHg) and on additional echocardiographic variables suggestive of PH.

1. Echocardiographic diagnosis: PH unlikely
   TR velocity < 2.8 m/s, systolic Ppa < 36 mmHg
   and no additional echocardiographic variables suggestive of PH

2. Echocardiographic diagnosis: PH possible
   TR velocity < 2.8 m/s, systolic Ppa < 36 mmHg,
   but presence of additional echocardiographic variables suggestive of PH
   TR velocity 2.9–3.4 m/s, systolic Ppa 37–50 mmHg
   with/without additional echocardiographic variables suggestive of PH

3. Echocardiographic diagnosis: PH likely
   TR velocity > 3.4 m/s, systolic Ppa > 50 mmHg,
   with/without additional echocardiographic variables suggestive of PH.
Evaluation of various empirical formulars for estimating mean PA pressure using systolic PA pressure in adult.
Chemla D - Chest - 01-MAR-2009; 135(3): 760-8

<table>
<thead>
<tr>
<th>Equations</th>
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<td>Two-pressure model</td>
<td>F1</td>
</tr>
<tr>
<td></td>
<td>F2</td>
</tr>
<tr>
<td></td>
<td>F3</td>
</tr>
<tr>
<td>Single pressure model</td>
<td>F4</td>
</tr>
<tr>
<td></td>
<td>F5</td>
</tr>
</tbody>
</table>

The most accurate formula was F4 (mean bias, 0.0 mm Hg). sPAP > 36 mm Hg could be used to diagnose PH (mPAP > 25 mm Hg) with a 97.9% sensitivity and 98.6% specificity.
Echocardiographic Determination of Mean Pulmonary Artery Pressure

Amr E. Abbas, MD, F. David Fortuin, MD, Nelson B. Schiller, MD, Christopher P. Appleton, MD, Carlos A. Moreno, BS, and Steven J. Lester, MD

We performed a simultaneous Doppler and invasive study to validate the role of Doppler-derived peak pulmonary regurgitant velocity as a reliable non-invasive measure of pulmonary artery mean pressure. Assessment of right atrial pressure, as shown in this study, enhances the use of this Doppler parameter as a correlate of pulmonary artery mean pressure. ©2003 by Excerpta Medica, Inc. (Am J Cardiol 2003;92:1373–1376)

mPAP = 4PRv² + RAP
In conclusion, TRPG/TVI provides a reliable estimation of PVR over a wide range in patients with PAH with various underlying causes. A TRPG/TVI >7.6 showed 85% sensitivity and 92% specificity for identifying patients in the poor-prognosis group.
The Pathology
of
the pulmonary vasculature
Pathologic change

- An extension of muscle into peripheral, normally nonmuscular arteries.
- Medial hypertrophy of normally muscular arteries occurs.
- Reduction in arterial concentration due to impaired growth of arterioles.
- Dilation complexes, plexogenic lesions, fibrinoid necrosis

- An increase in blood flow to the pulmonary circulation
- Mechanical stretching in the pulmonary vasculature

- Systemic-to-pulmonary arterial communication produces the progressive structural and histologic changes
Heath Edwards classification of pulmonary vascular changes

1. Grade I: medial hypertrophy.
2. Grade II: cellular intimal proliferation
3. Grade III: occlusive changes.
4. Grade IV: dilatation
5. Grade V: plexiform lesion.
6. Grade VI: acute necrotizing arteritis
The Heath-Edwards classification is less useful to characterize the earliest changes frequently seen in infants and children undergoing cardiac surgery.

A morphometric approach was studied by Rabinovitch et al, Haworth, and Haworth and Hislop. The morphometric approach quantifies and grades from A to C the degree of abnormal distal extension of smooth muscle, the thickness of the medial hypertrophy, the density of small PAs relative to the number of alveoli.

The results of the morphometric analysis of lung biopsy specimens may be predictive of late outcome, but lung biopsy is used rarely in the routine assessment of operability.
A morphometric approach was studied by Rabinovitch

<table>
<thead>
<tr>
<th>Grade</th>
<th>Structural finding</th>
<th>Hemodynamic finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Extension of muscle into peripheral arteries normally non muscular. Associated with a mild increase in the medial wall thickness of the normally muscular arteries(&lt;1.5 times normal)</td>
<td>Increased PBF Normal or minimal increased in mPAP Normal PVR</td>
</tr>
<tr>
<td>B</td>
<td>Extension as in Grade A but greater medial hypertrophy</td>
<td></td>
</tr>
<tr>
<td>mild</td>
<td>1.5 &lt; medial wall thickness &lt; 2</td>
<td></td>
</tr>
<tr>
<td>severe</td>
<td>2 &lt; medial wall thickness</td>
<td>Increased PBF Increased in mPAP Normal PVR</td>
</tr>
<tr>
<td>C</td>
<td>Future of B(severe) with a decrease number of peripheral arteries relative to alveoli and usually decreased arterial size</td>
<td>Increased PBF Increased in mPAP increased PVR</td>
</tr>
<tr>
<td>mild</td>
<td>more than half the normal number of arteries</td>
<td>3.5 Um²&lt;PVR&lt; 6 Um²</td>
</tr>
<tr>
<td>severe</td>
<td>Less than half the normal number of arteries</td>
<td>6 Um²&lt; PVR</td>
</tr>
</tbody>
</table>

The morphometric grading system evolved from correlation with preoperative pulmonary hemodynamic findings.
The Physiologic change of Pregnancy in Patients with PH

When it is complicated by pregnancy, it is associated with increased mortality, (mortality as high as 60%)

<table>
<thead>
<tr>
<th></th>
<th>Cardiac output(CO) increases by 50% from baseline.</th>
</tr>
</thead>
<tbody>
<tr>
<td>During pregnancy</td>
<td>1. Blood volume increases in the early stages,</td>
</tr>
<tr>
<td></td>
<td>2. A reduction in afterload secondary to decreased PVR.</td>
</tr>
<tr>
<td></td>
<td>3. Later in pregnancy, CO is augmented by an increase in HR.</td>
</tr>
<tr>
<td>During delivery</td>
<td>With every uterine contraction, approximately 500 mL of blood is diverted from the uterine to the maternal circulation, with a resultant increase in CO and BP.</td>
</tr>
<tr>
<td>After delivery</td>
<td>1. Significant autotransfusion from the uterine circulation.</td>
</tr>
<tr>
<td></td>
<td>2. Increase in venous return from the relief of vena caval obstruction by the gravid uterus.</td>
</tr>
<tr>
<td></td>
<td>3. With concomitant fluid shifts into the intravascular space,</td>
</tr>
<tr>
<td>In addition</td>
<td>Pregnancy is associated with a hypercoagulable state.</td>
</tr>
</tbody>
</table>
### ESC/ERS guidelines: hemodynamic definition of PH

<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics</th>
<th>Clinical group(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH</td>
<td>Ppa ≥ 25 mmHg</td>
<td></td>
</tr>
<tr>
<td>Pre-capillary PH</td>
<td>Ppa ≥ 25 mmHg</td>
<td>1. Pulmonary arterial hypertension</td>
</tr>
<tr>
<td></td>
<td>Ppcw ≤ 15 mmHg</td>
<td>2. PH due to lung disease</td>
</tr>
<tr>
<td></td>
<td>CO normal or reduced</td>
<td>3. Chronic thromboembolic PH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. PH with unclear and/or multifactorial mechanism</td>
</tr>
<tr>
<td>Post-capillary PH</td>
<td>Ppa ≥ 25 mmHg</td>
<td>2. PH due to left heart disease</td>
</tr>
<tr>
<td></td>
<td>Ppcw &gt; 15 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CO normal or reduced</td>
<td></td>
</tr>
</tbody>
</table>
The definition of PH on exercise as a $P_{pa} > 30$ mmHg is not supported by published data and healthy individuals can reach much higher values. Thus no definition for PH on exercise as assessed by RHC can be provided at the present time.

The Global Perspective Congenital Heart Disease: Pulmonary Vascular Disease: The Global Perspective. Ian Adatia Chest 2010;137;52S-61S
Figure: The timeline of drug approval in PAH is shown here, highlighting the advances in targeted drug therapy since the mid 1990s. VIP indicates vasoactive intestinal peptide; TKIs, tyrosine kinase inhibitors.
Figure 1. Schematic representation of pathways implicated in pulmonary arterial hypertension, and sites of action of current therapies.
Repair of previously inoperable patients who respond to advanced therapy

<table>
<thead>
<tr>
<th>For</th>
<th>Against</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Abort R-L shunt</td>
<td>1. Potential conversion of ES to IPHA (and thus worse long-term outcome)</td>
</tr>
<tr>
<td>2. Eliminate cerebrovascular event</td>
<td>2. High perioperative risk</td>
</tr>
<tr>
<td>3. Prevent cyanosis</td>
<td>3. Limited experience and no long term data</td>
</tr>
<tr>
<td>Increase Exercise capacity</td>
<td></td>
</tr>
<tr>
<td>Decrease erythrocytosis</td>
<td></td>
</tr>
<tr>
<td>Decrease hemostatic problem</td>
<td></td>
</tr>
<tr>
<td>Decrease systemic organ failure</td>
<td></td>
</tr>
<tr>
<td>4. Protective pulmonary circulation</td>
<td></td>
</tr>
</tbody>
</table>
# Prognostic Factors in PAH

<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)</td>
<td>6MWT</td>
<td>Shorter (&lt;300 m)</td>
</tr>
<tr>
<td>Peak O₂ consumption &gt;15 mL/min/kg</td>
<td>Cardio-pulmonary exercise testing</td>
<td>Peak O₂ 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</td>
<td>TAPSE² &gt;2.0 cm</td>
<td>Pericardial effusion</td>
</tr>
<tr>
<td>RAP &lt;8 mmHg and CI ≥2.5 L/min/m²</td>
<td>Echocardiographic findings²</td>
<td>RAP &gt;15 mmHg or CI ≤2.0 L/min/m²</td>
</tr>
</tbody>
</table>

² TAPSE: Tricuspid Annular Plane Echocardiographic Systolic Excursion