Evaluation of Patients with Pulmonary Hypertension

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The Prince Charles Hospital, Brisbane
The World at Night
Cyclone Yasi
A Land of contrasts and challenges!

Australia

January 2011

QLD
Description and definition

- **Pulmonary Hypertension**
  - elevated pressure in the pulmonary vascular bed, without specifying the location of the (vascular) pathology.

- **Pulmonary Arterial Hypertension**
  - elevated pressure in the pulmonary vascular bed, specifically ascribed to pathology in the pulmonary arterial tree.
Updated clinical classification of pulmonary hypertension
(4th PH World Symposium – Dana Point, CA – Feb 2008)

1. Pulmonary arterial hypertension
   1.1. Idiopathic PAH
   1.2. Heritable
      1.2.1. BMPR2
      1.2.2. ALK1, endoglin (with or w/o HHT)
      1.2.3. Unknown
   1.3. Drugs and toxins 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 haemolytic anaemia
   1.5. Persistent PH of the newborn

2. PH due to left heart diseases
   2.1. Systolic dysfunction
   2.2. Diastolic dysfunction
   2.3. Valvular disease

3. PH due to lung diseases and/or hypoxia
   3.1. COPD
   3.2. Interstitial lung diseases
   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 PH (CTEPH)

5. PH with unclear and/or multifactorial mechanisms
   5.1. Haematological disorders : myeloproliferative disorders, splenectomy.
   5.2. Systemic disorders, Sarcoidosis, pulmonary Langerhans cell histiocytosis, LAM, neurofibromatosis, vasculitis
   5.3. Metabolic disorders : Glycogen storage disease, Gaucher disease, Thyroid disorders
   5.4. Others : tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis.

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Definition of PAH by WHO
(Haemodynamic)

- Required:
  - Mean PAP ≥ 25 mmHg at rest
  - PAWP ≤ 15 mmHg

(note: no exercise or PVR criterion)

Pathophysiology of PAH

- Pre-symptomatic/Compensated
- Symptomatic/Decompensating
- Declining/Decompensated

Right Heart Dysfunction

Right Heart Failure

CO, PAP, PVR, RAP over Time
Consequences

- right ventricular hypertrophy
  - RV ischaemia

- right heart failure
  - systemic venous hypertension
  - syncope
  - low CO

- dyspnoea, dizziness, disability, death
Epidemiology
## PAH: not as rare as we once thought

<table>
<thead>
<tr>
<th></th>
<th>Prevalence (per million)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NIH Registry</strong></td>
<td></td>
</tr>
<tr>
<td>iPAH</td>
<td>1-2</td>
</tr>
<tr>
<td><strong>Scottish registry</strong></td>
<td></td>
</tr>
<tr>
<td>iPAH/fPAH</td>
<td>35</td>
</tr>
<tr>
<td>CTD PAH</td>
<td>22</td>
</tr>
<tr>
<td>CHD</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td><strong>72</strong></td>
</tr>
<tr>
<td><strong>French registry</strong></td>
<td></td>
</tr>
<tr>
<td>iPAH/fPAH</td>
<td>6.5</td>
</tr>
<tr>
<td>CTD PAH</td>
<td>2.3</td>
</tr>
<tr>
<td>CHD</td>
<td>1.7</td>
</tr>
<tr>
<td>Other</td>
<td>4.0</td>
</tr>
<tr>
<td>Total</td>
<td><strong>15</strong></td>
</tr>
</tbody>
</table>

The REVEAL Registry
An older population than once thought

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n=2525)</th>
<th>iPAH (n=1166)</th>
<th>CHD (n= 250)</th>
<th>CTD (n=639)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, mean ± SD</td>
<td><strong>50.1 ± 14.4</strong></td>
<td><strong>49.9 ± 14.8</strong></td>
<td><strong>41.6 ± 13.3</strong></td>
<td><strong>55.5 ± 13.4</strong></td>
</tr>
<tr>
<td>Female, %</td>
<td>79.5</td>
<td>80.3</td>
<td>73.6</td>
<td>90.1</td>
</tr>
<tr>
<td>WHO FC, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>7.6</td>
<td>8.3</td>
<td>5.7</td>
<td>5.7</td>
</tr>
<tr>
<td>II</td>
<td>36.7</td>
<td>36.4</td>
<td>38.3</td>
<td>32.2</td>
</tr>
<tr>
<td>III</td>
<td>50.0</td>
<td>49.7</td>
<td>51.5</td>
<td>54.9</td>
</tr>
<tr>
<td>IV</td>
<td>5.6</td>
<td>5.6</td>
<td>4.4</td>
<td>7.2</td>
</tr>
<tr>
<td>6MWD, m</td>
<td>366 ± 126</td>
<td>374 ± 129</td>
<td>382 ± 121</td>
<td>322 ± 120</td>
</tr>
<tr>
<td>PVR, wood units</td>
<td>21.1 ± 12.5</td>
<td>22.9 ± 11.4</td>
<td>23.7 ± 20.9</td>
<td>16.9 ± 9.1</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>9.1 ± 3.5</td>
<td>9.2 ± 3.5</td>
<td>8.9 ± 3.6</td>
<td>8.9 ± 3.5</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>2.4 ± 0.8</td>
<td>2.2 ± 0.8</td>
<td>2.7 ± 1.0</td>
<td>2.5 ± 0.8</td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>50.7 ± 13.6</td>
<td>52.1 ± 13.0</td>
<td>59.4 ± 16.9</td>
<td>44.9 ± 11.2</td>
</tr>
</tbody>
</table>

Diagnosis is late in the disease process


n=674

> 2 years from symptoms to dx

### Class II - baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=92)</th>
<th>bosentan (n=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean time from diagnosis, years</td>
<td>3.7</td>
<td>2.9</td>
</tr>
<tr>
<td>Etiology, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPH</td>
<td>58 (63%)</td>
<td>54 (58.1%)</td>
</tr>
<tr>
<td>CHD</td>
<td>16 (17.4%)</td>
<td>16 (17.2%)</td>
</tr>
<tr>
<td>SSc</td>
<td>5 (5.4%)</td>
<td>9 (9.7%)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (14.2%)</td>
<td>14 (15%)</td>
</tr>
<tr>
<td>Mean 6MWD, m ± SD</td>
<td>430.9 ± 91.9</td>
<td>442.5 ± 82.9</td>
</tr>
<tr>
<td>Mean PVR</td>
<td>802 ± 365</td>
<td>851 ± 535</td>
</tr>
<tr>
<td>dyn.sec.cm⁻⁵ ± sd</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Significant increase in PVR in placebo group over 6mo.

Treatment effect
-197 dyn.sec.cm$^{-5}$
$p<0.0001$

Placebo
$n = 92$

bosentan
$n = 93$
Why is it missed?

- Young patients with non-specific symptoms with a “normal” CXR and ECG
  - exercise induced “asthma”
  - chronic fatigue syndrome
  - depression

- Lack of practical therapy in earlier era lead to therapeutic nihilism

- Co-morbid conditions with similar symptoms
Functional class staging
WHO classification of functional status of patients with PAH

Class Description

I  No limitation of usual physical activity; ordinary physical activity does not cause dyspnoea, fatigue, chest pain, or presyncope

II  Mild limitation of physical activity; no discomfort at rest; but normal activity causes increased dyspnoea, fatigue, chest pain, or presyncope

III  Marked limitation of activity; no discomfort at rest but less than normal physical activity causes increased dyspnoea, fatigue, chest pain, or presyncope

IV  Unable to perform physical activity at rest; may have signs of RV failure; symptoms increased by almost any physical activity

ACCP Guidelines, CHEST 2004;126(1):
Survival
iPAH ("PPH")

Incidence: 1-2 per million

Female to male ratio 1.7:1

Typical age is 20-40 years

Median survival = 2.8 yrs

Mean survival of patients with PAH based on aetiology

Survival (%)

Years

0 1 2 3 4 5

0 20 40 60 80 100

CHD
Portopulmonary
iPAH
CTD
HIV

Predictors of outcome in PAH

- **Functional parameters**
  - 6-minute walk result
  - WHO Class IV status at diagnosis

- **Haemodynamic parameters**
  - pulmonary artery pressure
  - RA pressure
  - cardiac index
  - response to vasodilator challenge
    - linked to CCB response

- **Other**
  - Presence of pericardial effusion
  - BNP, uric acid

Rubin LJ. *Chest* 1993;104:236-250.
6MWD predicts survival at initial screening

Prognosis is related to functional class

- WHO FC IV: 6 months
- WHO FC III: 2.6 years
- WHO FC I/II: ~5 years

2.8 years median survival (natural history)

Early identification of PAH patients can help save lives

Natural history in the era of PAH-specific therapy

Survival (%) vs. Time (months)

- After 2000 Post-ERA*
- 1992–1999 Pre-ERA
- Before 1992 Pre-epoprosthenol

*ERA: Endothelin-receptor antagonist

Galie – survival according to drug mechanism

*Eur Heart J* 2009;30:394-403

-44%
Pathophysiology
## Risk factors for developing PAH

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Risk profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known genetic mutation predisposing PAH</td>
<td>20% chance of developing PAH</td>
</tr>
<tr>
<td>First degree relatives in a PAH family</td>
<td>10% chance of developing PAH</td>
</tr>
<tr>
<td>Scleroderma spectrum of disease</td>
<td>27% prevalence of PAH (RSVP &gt; 40 mmHg)</td>
</tr>
<tr>
<td>Portal hypertension associated with liver disease</td>
<td>5% prevalence of PAH (mPAP &gt; 25 mmHg and PVR &gt; 3.0 U)</td>
</tr>
<tr>
<td>CHD with systemic to pulmonary shunts</td>
<td>Approx. 100% in high flow, non-restrictive L-R shunts</td>
</tr>
<tr>
<td>Use of flenfluramine appetite suppressants</td>
<td>Prevalence of 136/million users based on odds ratio of 23x background</td>
</tr>
<tr>
<td>HIV infection</td>
<td>Prevalence 0.5/100</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>Prevalence 9.0/100 (TRV &gt; 3.0)</td>
</tr>
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</table>
Genetics of PAH

- Mutations in BMPR2 cause familial PAH
  - mutations detected in 55% of families
    - autosomal dominant
    - incomplete penetrance
  - 26% of “sporadic” cases (iPAH) have BMPR2 mutations

Genetics of PAH

- Other genetic factors
  - TGF-β superfamily

- HHT – other receptors
  - alk (activin receptor-like kinase) 1
  - endoglin
Diagnosis of PH
Reasons to suspect PH

- Unexplained dyspnoea and/or fatigue

- Typical symptoms and associated signs
  - Eg. Raynaud’s syndrome

- “At risk” conditions:
  - CREST, liver disease, HIV, sickle cell
  - Family history of PAH
  - History of stimulant/anorexigen use
Screening guidelines\textsuperscript{1-3}

Screening is appropriate in certain high-risk subgroups

- Doppler echo - followed by RHC to confirm the diagnosis of PAH

**High-risk groups**

- Congenital heart disease
- Connective tissue disease
- Sickle cell disease
- Family members with PAH
- Known genetic mutation

- Dyspnoea on exertion, angina (RV) or syncope that cannot be attributed to another cause

Screening can be effective in identifying disease at an earlier stage

No screening

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1%</td>
</tr>
<tr>
<td>II</td>
<td>24%</td>
</tr>
<tr>
<td>III</td>
<td>63%</td>
</tr>
<tr>
<td>IV</td>
<td>12%</td>
</tr>
</tbody>
</table>

With screening

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>44%</td>
</tr>
<tr>
<td>III</td>
<td>28%</td>
</tr>
<tr>
<td>IV</td>
<td>11%</td>
</tr>
</tbody>
</table>

Clinical history and physical exam

History
- high index of suspicion
- dyspnoea on exertion 60%
- fatigue, chest discomfort, dizziness, palpitations, syncope
- underlying conditions

Physical examination
- NB. *signs* occur late
  - accentuated P₂ 93%
  - TR murmur 40%
  - left parasternal heave
  - pulmonary regurgitation
  - Elevated systemic venous pressure
    - JVP
    - peripheral edema
    - hepatomegaly, ascites
    - unusual presentations
Electrocardiogram (ECG):
- Lacks sensitivity and specificity
- Normal in 13%
Chest X-ray

- Chest radiography (CXR)
  - Often "normal" in early stages
  - Enlargement of main pulmonary artery 90% and hilar vessels in 80%
  - Pruning in 51%
Echocardiogram

- Increased sPAP or TR jet
- Right atrial and ventricular hypertrophy
- Flattening of interventricular septum
- Small LV dimension
- Dilated PA
- Pericardial effusion
  - poor prognostic sign
  - venous pressure so high it impedes normal drainage from pericardium
  - do not drain, usually does not induce tamponade since RV under high-pressure and non-collapsible
Pulmonary function tests

- Obstructive or restrictive lung disease
- Diffusing capacity
- Screen for sleep disorders and nocturnal hypoxaemia
  - Not necessarily causative
  - Important contributor
Ventilation/perfusion (V/Q) scan and angiography

- V/Q scan is performed to exclude CTEPH.
- In CTEPH, at least one (and more commonly, several) segmental or larger mismatched ventilation-perfusion defects are present.
V/Q scan - CTEPH
Right-heart catheterisation

- **Diagnostic**
  - definitive diagnostic procedure
  - PAH vs. raised LAP – PAWP
  - saturation studies for CHD
  - pulmonary angiography (CTEPH)

- **Prognostic**
  - baseline measures: RAP, mPAP, CI, SvO₂
  - haemodynamic response to Rx (follow-up)
  - vasodilator responsiveness

- **Selection of therapy**
  - vasodilator challenge – Ca++ antagonists
  - PBAC requirements
Six-minute walk test (6MWT)

- Simple test that only requires a 30m hallway
- Self-paced
- Assesses a submaximal level of functional capacity
- Predictive equations
  - for males:
    - $6\text{MWD}(m) = 867 - (5.71 \text{ age, yrs}) + (1.03 \text{ height, cm})$
  - for females:
    - $6\text{MWD}(m) = 525 - (2.86 \text{ age, yrs}) + (2.71 \text{ height, cm}) - (6.22 \text{ BMI})$. 

ATS. Am J Respir Crit Care Med 2002;166:111-117.
PAH treatment modalities
How do we treat?

General measures:

- Avoid pregnancy
  - Contraception imperative
  - Maternal mortality 30%

- Immunizations for (respiratory) illnesses
  - Influenza & pneumococcal vaccinations
Classes of therapy

- **Medical**
  - Diuretics
  - and other treatment for RV dysfunction/failure
  - Anticoagulation (warfarin)
  - oxygen
  - **PAH-specific therapy**

- **Surgical**
  - atrial septostomy
  - lung transplantation
  - pulmonary endarterectomy (CTEPH)
Diuretics

- Principally to treat oedema from right heart failure
  - additional role of spironolactone?
- May need to combine classes
  - thiazide + loop diuretics
  - patients often require large and/or IV doses
- Avoid too much pre-load reduction
  - RV relies on Starling haemodynamics (cf. RV infarction)
Warfarin

- Studies only show benefit (survival) in iPAH patients

- Other PAH groups not as clear
  - expert opinion / extrapolation

- Generally, aim for INR 2.0-2.5

- Benefits thought to be
  - Reduction of in-situ thrombosis
  - Reduced DVT risk in low CO state
Oxygen

- Formal assessment of nocturnal and exertional oxygen levels
  - Minimize added insult of hypoxic vasoconstriction
  - Exclude comorbid obstructive sleep apnoea and hypoventilation syndromes

- Aim to keep oxygen saturation ≥90%
  - Often impossible with large right to left shunt
PAH specific therapies target specific pathways

- Endothelin pathway
  - Pre-proendothelin → Proendothelin
  - Endothelin receptor A
  - Endothelin-1
  - Endothelial cells

- Nitric oxide pathway
  - L-arginine → L-citrulline
  - Nitric oxide
  - cGMP
  - Exogenous nitric oxide
  - Phosphodiesterase type 5
  - Phosphodiesterase type 5 inhibitor

- Prostacyclin pathway
  - Arachidonic acid → Prostaglandin I₂
  - Prostacyclin (prostaglandin I₂)
  - cAMP
  - Prostacyclin derivatives

Vasodilatation and antiproliferation

PAH-specific therapies

- Calcium channel blockers
- Endothelin receptor antagonists (ERAs)
  - bosentan, ambrisentan
- Phosphodiesterase (type 5) inhibitors (PDE 5-I)
  - sildenafil, tadalafil
- Prostanoids
  - epoprostopenol, treprostinil, iloprost
WHO (Dana Point) PAH Treatment Algorithm

Oral anticoagulants (E/B) – IPAH/HPAH
Diuretics (E/A)
Oxygen* (E/A)
Digoxin (E/C)
Supervised rehabilitation (E/B)

Supportive therapy and general measures
Expert referral (E/A)

Avoid excessive physical exertion (E/A)
Birth control (E/A)
Psychological and social support (E/C)
Infection prevention (E/A)

Acute vasoreactivity test (A for IPAH)
(E/C for APAH)

WHO Class I-IV
Amlodipine, diltiazem, nifedipine (B)

Sustained response (WHO I-II)

WHO Class II
Ambrisentan, Bosentan, Sildenafil

WHO Class III
Ambrisentan, Bosentan, Epoprostenol IV, Iloprost inh, Sildenafil

WHO Class IV
Epoprostenol IV

Strength of Recommendation
A
B
C
E/B
E/C
Not approved

Sequential combination therapy

PDE-5 I + (B) Prostanoids + (B) ERA

INCOMPLETE CLINICAL RESPONSE
Atrial septostomy (E/B) and/or lung transplant (E/A)

Following response to therapy

- Six-minute walk test
- Echocardiogram
- Right heart catheterization
- Functional class
What’s on the Horizon?
Combination Therapy

- Emerging evidence of benefit

- prostanoid + ERA
- prostanoid + sildenafil
- bosentan + sildenafil
- triple therapy
Combination Therapy

- Current practice
  - sequential therapy

- Future trials
  - up front combinations
  - clinical target end points
    - haemodynamics
    - exercise
    - FC
Future directions

- VIP
- tyrosine kinase inhibition
  - imatinib
- genetic signalling
  - MAP kinase inhibitors
- proliferation signal inhibitors
  - SRL / ERL
Surgical options

- Atrial septostomy
- Transplantation
- Pulmonary endarterectomy
Atrial Septostomy

Rationale

- pressure overload $\rightarrow$ RV failure
  - septostomy functions as a “pressure valve”

- animal studies
  - increased systemic blood flow (+++ exercise)

- PPH patients with PFO have better prognosis
Atrial Septostomy

- Improvements
  - fall in RAP (response greater with higher RAP)
  - increase CO
  - decrease SaO₂ but increased SOT
  - improvement in RV systolic function

- survival / function
  - better up to 3 years
Transplantation

- Rarely performed for iPAH
  - SSC – trap for young players

- Any/all options have been used
  - Single lung tx difficult
  - Surgical preference
    - RV recovery in LTx

- 90% 1 year & 70% 5 year survival can be expected
Chronic Thrombo-Embolic Pulmonary Hypertension (CTEPH)
Background

- 3-5% of acute PE → CTEPH
- < 50% give history of diagnosed DVT/PE
- Most have single episode / incomplete resolution
- Months to years between event and symptoms
  - Secondary changes in vessel wall - ? irreversible
CTEPH - Survival

Riedel: *Chest* 1982; 81: 151-8
CTEPH

- Definitive surgical treatment:
  - pulmonary endarterectomy
    - mortality 5 -10% (< transplantation)
    - return to normal haemodynamics
Right Heart Haemodynamics

Assessment Day 0 Day 1 Day 2
RV Systolic RV EDP RV mean RAP mean
mm Hg

Graph showing changes in RV Systolic, RV EDP, RV mean, and RAP mean over time from Assessment to Day 2.
CTEPH - pre and post op

4 months post op
Summary

- Determine aetiology of PH
  - significant treatment implications
    - eg. CTEPH

- Differentiate PAH from other forms of PH
  - Don’t treat without a RHC
    - must confirm PAH
    - treatment implications if LV related
Summary

- Refer early to specialist centre
  - assessment
  - early effective therapy

- Treat aggressively, don’t settle for “stability”
  - current expert opinion