The Pulmonary Circulation: Pulmonary Embolism and Pulmonary Arterial Hypertension

Steven M. Kawut, M.D., M.S.
Lung Transplant Program
Division of Pulmonary, Allergy, and Critical Care Medicine
Department of Epidemiology
Columbia University
Pulmonary Vasculature

- Elastic pulmonary arteries (> 1-2 mm diameter)
- Muscular pulmonary arteries (100 μm-1 mm)
- Pulmonary arterioles (< 30 μm) no muscle
- 7 times more compliant than systemic vasculature

Ohm’s Law - \( V=IR \ldots \ R=V/I \)

- \( PVR= (mPA-LA)/CO \)
- 100 dynes/s/cm\(^5\)
- \( R=8 (\pi) \ n / r^4 \ \Pi \)
Control of the Pulmonary Circulation

- Hypoxia
- Nervous
- Neurohormones

Pulmonary Hypertension

Increased pulmonary arterial pressure
- usually increased PVR
- Vasoconstriction
- Obstruction
- Obliteration
- Cor pulmonale
Acute Pulmonary Embolism

- Deep venous thrombosis is precursor
  - 5 mil DVT, 10% have PE, 10% die
- After embolus hits-
  - Alveolar dead space created
  - Hyperventilation ensues
  - Arterial hypoxemia ensues
    - Increased A-V difference from RV strain and decreased CO
    - Shunt (pulmonary or cardiac)
    - Increased PA pressure, hypoxic vasoconstriction is overcome and V/Q mismatch occurs
  - Late- loss of surfactant and reperfusion

Normal V/Q Matching
Acute PE

Ventilation or blood flow L/min

Ventilation - perfusion ratio

O.U.

$V_e = 13.2 \text{ L/min}$

$CO = 3.7 \text{ L/min}$

Shunt 20%

Dead Space 42%

Acute PE

Ventilation or blood flow L/min

Ventilation - perfusion ratio

B.D.

$V_e = 17.0 \text{ L/min}$

$CO = 3.7 \text{ L/min}$

Shunt 39%

Dead Space 69%
Acute Pulmonary Embolism

- Obstruction by thrombus
  - < 20% ok
  - 30-40% less ok
  - > 40-50% - bad

- Response
  - No preexisting disease
  - Preexisting disease

Acute Pulmonary Embolism

- Symptoms
  - Dyspnea
  - Chest pain
  - Syncope

- Signs
  - Tachypnea
  - Tachycardia
  - Rales
  - RV findings
  - Legs
Acute Pulmonary Embolism

- **Diagnosis**
  - D-dimer
  - Chest radiograph
  - Ecg
  - Arterial blood gas
  - Duplex ultrasound
  - Ventilation-perfusion scan
  - CT scan of the chest with contrast

- **Treatment**
  - Heparin, warfarin- get therapeutic within 24 hours
  - Thrombolytic therapy
  - Inferior vena cava filter
Normal Pulmonary Artery Pressures

WHO Classification

- Pulmonary arterial hypertension
- Pulmonary hypertension with left heart disease
- Pulmonary hypertension associated with lung diseases and/or hypoxemia
- Pulmonary hypertension due to chronic thrombotic and/or embolic disease
- Miscellaneous

(Simonneau, JACC, 2004)
WHO Classification

- **Left Heart Disease**
  - Atrial
  - Ventricular
  - Valvular

- **Hypoxemic**
  - COPD
  - ILD
  - Sleep-disordered breathing
  - Alveolar hypoventilation
  - High altitude
  - Developmental abnormalities

- **Thrombotic/embolic**

- **Miscellaneous**

(Simonneau, JACC, 2004)

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WHO Classification

- **Pulmonary arterial hypertension**
  - Idiopathic
  - Familial
  - Associated with:
    - Drugs/Anorexigen use ("Fen-phen")
    - Collagen vascular disease
    - HIV infection
    - Portal hypertension
    - Congenital systemic-to-pulmonary cardiac shunts
    - Other (glycogen storage dis, HHT, splenectomy)
  - Associated with significant venous or capillary involvement (PVOD, PCH)

(Simonneau, JACC, 2004)
Normal

Pathology

Endothelial thickening

Smooth muscle hypertrophy
Pathology

Plexiform lesions

In situ thrombosis

Newman, 2004
Bone Morphogenetic Protein Receptor-II

- TGF-β receptor superfamily, Chr 2q 31-33
- Heterozygous germ line mutation: frameshift, nonsense, and missense
- 25-50% of familial; 26% of sporadic cases
  (Thompson, J Med Gen, 2000; Machado, Am J Hum Gen, 2001)
- Inheritance: autosomal dominant
- Incomplete penetrance, genetic anticipation
- Mechanism: haplotype insufficiency vs. dominant negative

Medical History and Labs

- Past medical history
- Exposures
- Drug use
- Family history
- Anti-nuclear antibodies
- HIV
- Anti-phospholipid antibodies
<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Lung Function and Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chest radiograph</td>
<td>• Chest radiograph</td>
</tr>
<tr>
<td>• Electrocardiogram</td>
<td>• Arterial blood gas</td>
</tr>
<tr>
<td>• Pulmonary function testing</td>
<td>• High-resolution CT scan</td>
</tr>
<tr>
<td>• Cardiopulmonary exercise testing</td>
<td>• V/Q scan</td>
</tr>
<tr>
<td>• Arterial blood gas</td>
<td>• Pulmonary function testing</td>
</tr>
<tr>
<td>• HIV testing</td>
<td>• Polysomnography</td>
</tr>
<tr>
<td>• Serologies</td>
<td>• Right heart catheterization</td>
</tr>
<tr>
<td>• High-resolution computed tomography</td>
<td>• Echocardiography</td>
</tr>
<tr>
<td>• Polysomnography</td>
<td>• Pulmonary angiography</td>
</tr>
<tr>
<td>• V/Q scan</td>
<td>• Arterial blood gas</td>
</tr>
<tr>
<td>• Pulmonary angiography</td>
<td>• HIV testing</td>
</tr>
<tr>
<td>• Echocardiography</td>
<td>• Serologies</td>
</tr>
<tr>
<td>• Right heart catheterization</td>
<td>• Pulmonary arteriogram</td>
</tr>
</tbody>
</table>
Echocardiography

- Tricuspid regurgitation
- Right a/v dilatation
- Right ventricular hypertrophy
- Right ventricular dysfunction
- Pulmonic insufficiency
- Intracardiac shunt
- Left heart
- Valvular morphology
- Pericardial effusion

Right Heart Catheterization

- Diagnose pulmonary hypertension with normal PCWP
  - Assess severity of pulmonary hypertension
  - Assess acute vasoreactivity
Right Heart Catheterization

- Mean right atrial pressure
- Mean pulmonary artery pressure
- Cardiac index
- Acute vasoreactivity

RA-4 mm Hg
PA- 90/60 mm Hg
PCWP- 8 mm Hg
CI- 2.4 L/m/m²
PVR- 1100 d•s•cm⁻⁵

RA-12 mm Hg
PA- 50/25 mm Hg
PCWP- 8 mm Hg
CI- 1.0 L/m/m²
PVR- 1100 d•s•cm⁻⁵
Therapy Targets for PAH

Therapies for PAH

- Preventative care
- Anticoagulation
- Supplemental oxygen
- Diuretics
- Inotropes
- Calcium channel blockers
- Prostacyclin analogues
- Endothelin-1 receptor antagonists
- PDE-5 inhibitors
- Cardiopulmonary rehabilitation
- Atrial septostomy
- Lung transplantation


![Graph showing survival rates with and without warfarin](Kawut, 2005)

\[ p = 0.02 \]
Intravenous Epoprostenol

Randomized, controlled trial, IPAH
NYHA III-IV
41 randomized to IV epoprostenol + conventional therapy
40 randomized to conventional therapy alone
All but 1 in each group were anticoagulated

(Barst, 1996)
Change from Baseline in 6-Minute Walk Test

Week 1          Weeks 8 and 12 (Mean)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Conv (N=40)</th>
<th>Conv + Epo (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA, mm Hg</td>
<td>0.1 (1)</td>
<td>-2.2 (1)*</td>
</tr>
<tr>
<td>mPA, mm Hg</td>
<td>1.9 (2)</td>
<td>-4.8 (1)*</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>-0.2 (0.1)</td>
<td>0.3 (0.1)*</td>
</tr>
<tr>
<td>PVR, d•s•cm⁻⁵</td>
<td>120 (80)</td>
<td>-272 (56)*</td>
</tr>
</tbody>
</table>

*P< 0.05

Changes from Baseline to 12 Weeks

(Barst, 1996)
Survival on Epoprostenol

![Graph showing survival rates compared to conventional treatment.](Barst, 1996)

**Cumulative Survival (%)**
- 100
- 90
- 80
- 70
- 60
- 50
- 40
- 30
- 20
- 10
- 0

**Months**
- 0
- 1
- 2
- 3

**Epo**
- Conventional Rx

$p=0.003$

**Serious Complications**

- Catheter-related infections
- Malfunction of the drug delivery system
- Systemic hypotension
- Ascites
- Coronary steal
- Thrombocytopenia

(Barst, 1996)
Inhaled Iloprost (AIR)

- Randomized, double-blind, placebo-controlled
- 12 weeks inhaled iloprost vs. placebo
- 203 patients, NYHA Class III or IV
  - IPAH (50%)
  - Associated with connective tissue disease (17%) or anorexigen use (4.5%)
  - Chronic thromboembolic PH (28%)


Inhaled Iloprost (AIR)

- 2.5 or 5 mcg, 6 to 9 times/day while awake
- median inhaled dose, 30 mcg/day
- mean inhalations/day = 7.3
- 90% of patients never inhaled iloprost during sleeping hours

Inhaled Iloprost: *Composite Primary Endpoint*

Composite response definition: 6 minute walk 10% increase plus NYHA class improvement without death or clinical worsening

Inhaled Iloprost: *PAH Patients*

Placebo-corrected mean difference at 12 weeks = 40 meters (p<0.01)
Prostacyclin Analogues—IV Epo, Iloprost, Treprostinil

Findings:
- Different ∆ 6MWT over short term
- Different ∆ dyspnea over 12 weeks
- Improved time to clinical endpoints (epo, ilo)

Problems:
- Success of masking subjects, investigators
- Variable hemodynamic benefits
- No clear survival benefits
- Suboptimal delivery systems

Therapy Targets for PAH

BREATHE-1
Bosentan Randomized Trial of Endothelin Receptor Antagonist Therapy for Pulmonary Hypertension

11 countries, 27 sites randomized 214 patients from mid-July 2000 to Dec 2000
Patients were rolled over to an Open-Label study (n=198)

(Brubin, 2002)
Slide courtesy of Actelion

BREATHE-1:
Main Inclusion Criteria

- Males or females ≥ 12 years old
- PAH:
  • Idiopathic
  • Connective tissue or autoimmune diseases such as scleroderma (SSc/PHT) or systemic lupus erythematosus (SLE)
- WHO Class III-IV
- Baseline 6 minute walk test of ≥ 150 m and ≤ 450 m

(Rubin, 2002)
Slide courtesy of Actelion
**BREATHE-1: Study Design**

- **Screening**
  - Placebo
  - Bosentan 62.5 mg bid
- **Period 1 – Evaluation Period**
  - Placebo
  - Bosentan 250 mg bid
  - Bosentan 125 mg bid
- **End-point: Week 16**

- **Period 2 – Follow-up Period**
  - 3 months

**6-Minute Walk Test**

- Change From Baseline to Week 16
- **Δ Walk Distance (meters)**
- **Placebo (n = 69)**
- **Bosentan (n = 144)**
- **Mean ± SEM**
- **P = 0.0002**

- **Baseline**
- **Week 4**
- **Week 8**
- **Week 16**

**Dosages**
- 62.5 mg bid
- 125 or 250 mg bid

(Rubin, 2002)

Slide courtesy of Actelion
**BREATHE-1: Results**

**Time to Clinical Worsening**

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Event-Free (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>75%</td>
</tr>
<tr>
<td>8</td>
<td>50%</td>
</tr>
<tr>
<td>12</td>
<td>25%</td>
</tr>
<tr>
<td>16</td>
<td>95%</td>
</tr>
<tr>
<td>20</td>
<td>75%</td>
</tr>
<tr>
<td>24</td>
<td>63%</td>
</tr>
<tr>
<td>28</td>
<td>89%</td>
</tr>
</tbody>
</table>

- **Bosentan (n = 144)**
- **Placebo (n = 69)**

*pp = 0.0015, pp = 0.0038*

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**Endothelin Receptor Antagonists**

**Findings:**
- Different ∆ 6MWT over short term
- Different ∆ hemodynamics over short term

**Questions:**
- No clear benefit on survival, transplant, or epo
- ET-A vs. dual receptor antagonism?
- Durability of effects?
- Is combination therapy effective?
Therapy Targets for PAH


- Phosphodiesterase type 5 inhibitor
- Exogenous nitric oxide
- Endothelin receptor antagonists
- Prostacyclin derivatives
- Endothelin receptor A
- Endothelin 1
- Nitric oxide
- Prostacyclin (prostaglandin I2)
- Endothelin receptor B

Vasodilation and antiproliferation
Vasoconstriction and proliferation

cGMP
cAMP

L-arginine → L-citrulline

Phosphodiesterase type 5

- PAH due to:
  - Idiopathic
  - Connective tissue disease
  - CHD
  - Baseline 6 minute walk test of ≥ 100 m and ≤ 450 m

- 53 centers
- Placebo, 20, 40, 80 mg TID
- 360 patients screened, 278 randomized

(Silvestri, 2005)
Table 2.  Mean Change in Hemodynamic Variables from Baseline to Week 12.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N=69)</th>
<th>Sildenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate — beats/minute</td>
<td>-1.3 (-4.1 to 1.4)</td>
<td>-3.7 (-5.9 to -1.6)</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure — mm Hg</td>
<td>0.8 (-0.8 to 2.3)</td>
<td>-2.1 (-4.3 to -0.0)</td>
</tr>
<tr>
<td>Cardiac index — liters/min/m²</td>
<td>-0.92 (-0.17 to 0.31)</td>
<td>0.21 (0.04 to 0.38)</td>
</tr>
<tr>
<td>Pulmonary vascular resistance — dyn-sec-cm⁻⁵</td>
<td>-2.12 (-2.17 to -2.7)</td>
<td>-1.40 (-2.18 to -0.9)</td>
</tr>
<tr>
<td>Right atrial pressure — mm Hg</td>
<td>-0.3 (-0.9 to 1.5)</td>
<td>-0.8 (-1.9 to 0.3)</td>
</tr>
</tbody>
</table>
ADULT LUNG TRANSPLANTATION
Actuarial Survival By Diagnosis (1990-2001)

Table 1: Incidence of Clinical Worsening and of the Most Frequent Adverse Events in the Placebo and Sildenafil Groups.

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N=70)</th>
<th>Sildenafil (N=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 mg (N=69)</td>
<td>40 mg (N=67)</td>
</tr>
<tr>
<td></td>
<td>60 mg (N=67)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>number (percent)</td>
<td></td>
</tr>
<tr>
<td>Clinical worsening</td>
<td>7 (10)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hospitalization for pulmonary arterial hypertension</td>
<td>7 (10)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Initiation of prostacyclin</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Initiation of bosentan</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adverse event†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>27 (39)</td>
<td>12 (44)</td>
</tr>
<tr>
<td>Shivering</td>
<td>3 (4)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (7)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Back pain</td>
<td>8 (11)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (6)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Limb pain</td>
<td>4 (6)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>6 (8)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>10 (14)</td>
<td>12 (17)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (3)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (1)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastrectasis</td>
<td>0</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

α1-antitrypsin (N=1,288)
Cystic Fibrosis (N=1,809)
Emphysema/ COPD (N=4,643)
IPF (N=1,981)
PPH (N=714)
Sarcoidosis (N=303)
Therapy for PAH
Functional class II/III/IV(1)

General Care
Oral anticoagulants (B for IPAH, E/C for other PAH) + diuretics + oxygen (E/A) + digoxin

Acute Vasoreactivity Testing (A for IPAH, E/C for PAH)(2)

Positive
Oral CCB (B for IPAH, E/B for other PAH)
Sustained Response(3)
Yes
No
Continue CCB

Negative
Functional Class III (5)
Endothelin Receptor Antagonists
bosentan (A)
or
Chronic IV epoprostenol (A)
or
Prostanoid Analogues
SQ treprostinil (B) 
Inhaled iloprost (B), beraprost (I)
PDE-5 Inhibitors
(sildenafil) (C)(6)

Functional Class IV(4)
Chronic IV epoprostenol (A)
bosentan (B)
treprostinil (B)
Chronic IV iloprost (C)
No improvement or deterioration
Atrioseptostomy + Lung Transplantation


Survival in Pulmonary Arterial Hypertension

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Years 1</th>
<th>Years 2</th>
<th>Years 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH1 (1981-1985)</td>
<td>68%</td>
<td>~58%</td>
<td>48%</td>
</tr>
<tr>
<td>New York2 (1994-2002)</td>
<td>87%</td>
<td>77%</td>
<td>75%</td>
</tr>
<tr>
<td>Chicago3 (1991-2001)</td>
<td>88%</td>
<td>76%</td>
<td>63%</td>
</tr>
<tr>
<td>Nashville4 (1995-2001)</td>
<td>85%</td>
<td>76%</td>
<td>65%</td>
</tr>
<tr>
<td>Philadelphia5 (1997-2001)</td>
<td>84%</td>
<td>71%</td>
<td>71%</td>
</tr>
<tr>
<td>Clamart6 (1992-2001)</td>
<td>85%</td>
<td>70%</td>
<td>63%</td>
</tr>
<tr>
<td>Germany7 (1996-2001)</td>
<td>68%</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

1D’Alonzo, Ann Int Med, 1991
2Kawut, AJC, 2005
3McLaughlin, Circ, 2002
4Kuhn, AJRCCM, 2003
5Kavut, Chest, 2003
6Sitbon, JACC, 2002
7Wensel, Circ, 2002
Survival Determinants of Patients with PAH at New York Presbyterian Hospital (1994-2002)

Retrospective cohort study of 84 consecutive adult patients

- Mean age: 42 (14) years
- Female: 68 (81%)
- Hispanic: 9 (11%) Black: 6(7%) Asian: 9 (11%)
- IPAH: 66 (78%) Familial: 14 (17%) Anorexigen: 4 (5%)
- IV Epoprostenol: 38 (45%)
- SC Treprostinil: 12 (14%)
- Bosentan: 23 (27%)
- Warfarin: 79 (94%)
- Digoxin: 72 (86%)

(Kawut, AJC, 2005)

Kaplan-Meier Survival Estimate
### Hemodynamic Survival Determinants

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>1.06</td>
<td>1.02-1.1</td>
<td>0.005</td>
</tr>
<tr>
<td>SvO$_2$</td>
<td>0.94</td>
<td>0.90-0.98</td>
<td>0.003</td>
</tr>
<tr>
<td>RA</td>
<td>1.05</td>
<td>0.99-1.1</td>
<td>0.09</td>
</tr>
<tr>
<td>mPA</td>
<td>1.02</td>
<td>0.98-1.05</td>
<td>0.29</td>
</tr>
<tr>
<td>CI</td>
<td>0.36</td>
<td>0.17-0.76</td>
<td>0.005</td>
</tr>
<tr>
<td>PVRI</td>
<td>1.03</td>
<td>1.01-1.03</td>
<td>0.005</td>
</tr>
<tr>
<td>Acute vasoreactivity</td>
<td>0.11</td>
<td>0.01-0.81</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*(Kawut, AJC, 2005)*

### Multivariate Survival Model

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black or Asian</td>
<td>4.3</td>
<td>1.7-11</td>
<td>0.002</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>0.37</td>
<td>0.16-0.84</td>
<td>0.031</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>0.35</td>
<td>0.12-0.99</td>
<td>0.05</td>
</tr>
<tr>
<td>CI</td>
<td>0.41</td>
<td>0.19-0.90</td>
<td>0.026</td>
</tr>
<tr>
<td>Acute vasoreactivity</td>
<td>0.13</td>
<td>0.02-0.96</td>
<td>0.046</td>
</tr>
</tbody>
</table>

*(Kawut, AJC, 2005)*
Conclusions

Identification of BMPR2 has changed the paradigm of disease in PAH.

There are new effective therapies for PAH.

Innovative treatments may be on the horizon.

Survival has improved for patients with PAH.

Right heart function continues to be a primary determinant of outcome.

Reactivity of the pulmonary vascular bed is a phenotype which portends good outcomes.

What is the Future of Treatment of Pulmonary Arterial Hypertension?

Better Prediction of Outcomes

Innovative and Combination Therapies

Improvements in Outcome after Lung Transplantation

Anti-platelet therapies