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: $V=IR$, $R=V/I$

- $PVR = (mPA-LA)/CO$
- $100$ dynes/s/cm$^5$
- $R = \frac{l}{\pi r^4}$

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 ml 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

```
[Diagram showing normal V/Q matching]
```

Acute PE

```
[Diagram showing acute PE]
```

**Ventilation - blood flow ratio**
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

[Diagram of 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

- Thrombotic/embolic
  - Hypoxemic
  - COPD
  - ILD
  - Sleep-disordered breathing
  - Alveolar hypoventilation
  - High altitude
  - Developmental abnormalities

- Miscellaneous

(Simonneau, JACC, 2004)

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
Bone Morphogenetic Protein Receptor-II

Columbia (Deng et al., Am J Hum Gen, 2000)
Vanderbilt (Lane et al., Nat Gen, 2000)

- 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
Evaluation

- Chest radiograph
- Electrocardiogram
- Pulmonary function testing
- Cardiopulmonary exercise testing
- Arterial blood gas
- HIV testing
- Serologies
- High-resolution computed tomography
- Polysomnography
- V/Q scan
- Pulmonary angiography
- Echocardiography
- Right heart catheterization

Lung Function and Imaging

- Chest radiograph
- High-resolution CT scan
- V/Q scan
- Pulmonary arteriogram
- Arterial blood gas
- Pulmonary function testing
- Polysomnography

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

Right Heart Catheterization

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

- RA-12 mm Hg
- PA- 50/25 mm Hg
- PCWP- 8 mm Hg
- CI- 1.0 L/min/m²
- PVR- 1100 d•cm•s
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

Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 Years
Warfarin
No warfarin
p = 0.02

• Urine 11-dehydro-TxB₂ (TxM)
• Urine 2,3-dinor-6-keto-PGF₁α (PGI-M)

Arachidonic acid
PGI₂
PGH₂
COX
Platelets
TxM
TxA₂
Thromboxane
PGL₂
PGI₂
Prostacyclin

Endothelium

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

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

![Graph showing change in meters for Epoprostenol and Conventional Therapy](image)

*(Barst, 1996)*

**Changes from Baseline to 12 Weeks**

<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* *(Barst, 1996)*

**Survival on Epoprostenol**

![Graph showing cumulative survival in months for Conventional Rx and Epo](image)

*p=0.003* *(Barst, 1996)*
Serious Complications

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

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

- 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

Pre-proendothelin $\rightarrow$ Proendothelin
L-arginine $\rightarrow$ L-citrulline
Arachidonic acid $\rightarrow$ Prostaglandin I2

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)

BREATHE-1: Main Inclusion Criteria

- Males or females $\geq 12$ 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 $\geq 150$ m and $\leq 450$ m

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

- **Period 1** - Evaluation Period
  - Screening
  - Placebo
  - Bosentan 62.5 mg bid
  - Bosentan 250 mg bid

- **Period 2** - Follow-up Period
  - 1 month
  - 3 months
  - 3 months

- **Randomization**
- **End-point** - Week 16

**Changes in 6-Minute Walk Test**

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

**Results**

- **Time to Clinical Worsening**
  - Bosentan (n = 144)
  - Placebo (n = 69)
- **95%**
- **99%**

**Slide courtesy of Actelion**
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


Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension

- 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

(Galie, 2003)
ADULT LUNG TRANSPLANTATION
Actuarial Survival By Diagnosis (1990-2001)

Therapy for PAH

Functional class III/IV

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)(1)

Functional Class III

Endothelin Receptor Antagonists

Positive

Negative

Sustained Response(3)

Yes

No

Contrast CCB

Chronic IV epoprostenol (A)

Bosentan (B)

Treprostinil (B)

Chronic IV iloprost (C)

Endothelin Receptor Antagonists

Bosentan (A)

Or

Chronic IV epoprostenol (A)

Or

Prostanoid Analogues

SQ treprostinil (B)

Inhaled iloprost

Chronic IV iloprost (C)

PDE-5 Inhibitors

Sildenafil (C)

Atrioseptostomy + Lung Transplantation


Survival in Pulmonary Arterial Hypertension

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Years</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH(1981-1985)</td>
<td></td>
<td>68%</td>
<td>~58%</td>
<td>48%</td>
</tr>
<tr>
<td>New York(1994-2002)</td>
<td></td>
<td>87%</td>
<td>77%</td>
<td>75%</td>
</tr>
<tr>
<td>Chicago(1991-2001)</td>
<td></td>
<td>88%</td>
<td>76%</td>
<td>63%</td>
</tr>
<tr>
<td>Nashville(1995-2001)</td>
<td></td>
<td>85%</td>
<td>76%</td>
<td>65%</td>
</tr>
<tr>
<td>Philadelphia(1997-2001)</td>
<td></td>
<td>84%</td>
<td>71%</td>
<td>71%</td>
</tr>
<tr>
<td>Clamart(1992-2001)</td>
<td></td>
<td>85%</td>
<td>70%</td>
<td>63%</td>
</tr>
<tr>
<td>Germany(1996-2001)</td>
<td></td>
<td>68%</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>


1 D'Alonzo, Ann Int Med, 1991
2 Kawut, AJC, 2005
3 McLaughlin, Circ, 2002
4 Kuhn, AJRCCM, 2003
5 Kawut, Chest, 2003
6 Sitbon, JACC, 2002
7 Wensel, 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>Variable</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>SvO₂</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>0.98-1.1</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>0.01-1.81</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