The Pulmonary Circulation: Pulmonary Embolism and Pulmonary Arterial Hypertension

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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: \( \frac{(mPA-LA)}{CO} \)
100 dynes/s/cm²
\( R=8 (l) n / r^4 \Pi \)

Control of the Pulmonary Circulation

- Hypoxia
- Nervous
- Neurohormones

Pulmonary Vasculature

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

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

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)

Normal Pulmonary Artery Pressures

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 (glucagon 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

- 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
- RA-12 mm Hg
- PA- 50/25 mm Hg
- PCWP-8 mm Hg
- CI- 2.4 L/min/m²
- CI- 1.0 L/min/m²
- PVR- 1100 dynes/cm²
- PVR-1100 dynes/cm²
Therapy Targets 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

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
Change from Baseline in 6-Minute Walk Test

<table>
<thead>
<tr>
<th>Variable</th>
<th>Conv (N=40)</th>
<th>Conv + Epo (N=41)</th>
<th>P&lt;0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA, mm Hg</td>
<td>0.1 (1)</td>
<td>-2.2 (1)*</td>
<td></td>
</tr>
<tr>
<td>mPA, mm Hg</td>
<td>1.9 (2)</td>
<td>-4.8 (1)*</td>
<td></td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>-0.2 (0.1)</td>
<td>0.3 (0.1)*</td>
<td></td>
</tr>
<tr>
<td>PVR, d•s•cm⁻⁵</td>
<td>120 (80)</td>
<td>-272 (56)*</td>
<td></td>
</tr>
</tbody>
</table>

Serious Complications

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

Changes from Baseline to 12 Weeks

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%)

Survival on Epoprostenol

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

*P<0.05 (Barst, 1996)

Inhaled Iloprost: Composite Primary Endpoint

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

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>Iloprost</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-minute walk 10% increase 30 min. after inhalation</td>
<td>10%</td>
<td>43%</td>
<td>0.0033</td>
</tr>
<tr>
<td>NYHA Class improvement</td>
<td>25%</td>
<td>25%</td>
<td>4%</td>
</tr>
<tr>
<td>Death or worsening</td>
<td>13%</td>
<td>19%</td>
<td>4%</td>
</tr>
<tr>
<td>Composite clinical endpoint</td>
<td>0%</td>
<td>19%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Inhaled Iloprost: PAH Patients

Placebo-corrected mean difference at 12 weeks = 40 meters (p<0.01)

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

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

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)

Prostacyclin pathway
- Pre-proendothelin Æ Proendothelin
- L-arginine Æ L-citrulline
- Arachidonic acid Æ Prostaglandin I2
- Endothelin pathway
- Endothelin 1
- Endothelin receptor A
- Endothelin receptor B
- Vasodilation and antiproliferation

Phosphodiesterase type 5 inhibitor
- cGMP
- cAMP

Exogenous nitric oxide
- Nitric oxide
- Endothelial cells
- Vessel lumen

Therapy Targets for PAH

BREATHE-1: Study Design

<table>
<thead>
<tr>
<th>Period 1 – Evaluation Period</th>
<th>Period 2 – Follow-up Period</th>
<th>Baseline &amp; randomization</th>
<th>End-point: Week 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Bosentan 125 mg bid</td>
<td>Bosentan 250 mg bid</td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>3 months</td>
<td>3 months</td>
<td></td>
</tr>
</tbody>
</table>

BREATHE-1: Results

Time to Clinical Worsening

<table>
<thead>
<tr>
<th>Event-Free (%)</th>
<th>Time (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>95%</td>
<td>4</td>
</tr>
<tr>
<td>89%</td>
<td>8</td>
</tr>
<tr>
<td>83%</td>
<td>12</td>
</tr>
<tr>
<td>75%</td>
<td>16</td>
</tr>
<tr>
<td>63%</td>
<td>20</td>
</tr>
<tr>
<td>56%</td>
<td>24</td>
</tr>
<tr>
<td>42%</td>
<td>28</td>
</tr>
</tbody>
</table>

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

- 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

(Bukos, 2005)
ADULT LUNG TRANSPLANTATION
Actuarial Survival By Diagnosis (1990-2001)

Survival (%)
0 25 50 75 100

Years Post-Transplantation
0 1 2 3 4 5 6 7

- Phthisis
- 30 mg of sildenafil
- 40 mg of sildenafil
- 60 mg of sildenafil

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N=</th>
<th>Years Post-Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-1 Antitrypsin</td>
<td>1,288</td>
<td></td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>1,809</td>
<td></td>
</tr>
<tr>
<td>Emphysema/COPD</td>
<td>4,643</td>
<td></td>
</tr>
<tr>
<td>IPF</td>
<td>1,981</td>
<td></td>
</tr>
<tr>
<td>PPH</td>
<td>714</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>303</td>
<td></td>
</tr>
</tbody>
</table>

Therapy for PAH
Functional class 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)
- Therapies for PAH
  - Functional class II/III/IV (A)
  - General Care
  - Oral anticoagulants (B for IPAH, E/C for other PAH)
  - Continue 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 (B), beraprost (l)
  - PDE-5 Inhibitors (sildenafil) (C) (6)

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>Clarivate (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>

*Data from: Ann Int Med, 1991
*Kawan, AJRCCM, 2003
*Koeln, JACC, 2002
*Kawan, Chest, 2003
*Koeln, 1995-2001
*Chicago, 1991-2001
*New York, 1994-2002
*San Francisco, 1991-2001
*Clarivate, 1992-2001
*Germany, 1996-2001

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

Survival

0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00

Years

0 1 2 3 4 5 6 7 8 9 10

N= 84 65 45 36 26 13 8 3 1 1 --

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)

Hemodynamic Survival Determinants

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>SvO2</td>
<td>0.94</td>
<td>0.90-0.98</td>
</tr>
<tr>
<td>RA</td>
<td>1.05</td>
<td>0.99-1.1</td>
</tr>
<tr>
<td>mPA</td>
<td>1.02</td>
<td>0.98-1.05</td>
</tr>
<tr>
<td>CI</td>
<td>0.36</td>
<td>0.17-0.76</td>
</tr>
<tr>
<td>PVRI</td>
<td>1.03</td>
<td>1.01-1.03</td>
</tr>
<tr>
<td>Acute vasoreactivity</td>
<td>0.11</td>
<td>0.01-0.81</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