Pulmonary Hypertension in Congenital Heart Disease
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Associate Professor of Pediatrics and Medicine
Overview

• Adult Congenital Heart Disease in the U.S.
• Pulmonary Arterial Hypertension (PAH) Review
• PAH and Congenital Heart Disease trials
  – BREATHE-5
  – SERAPHIN
• ACHD cases
Topics NOT discussed

Instagram

the Real Housewives

The Finals
Adult Congenital Heart Disease: An Emerging Field in Cardiology (...even in Hollywood!)

*Top 3 movie titles for ACHD*
No. 3
No. 1 movie title for ACHD
The Hemodynamic “Working” Definition of Pulmonary Arterial Hypertension  (in adults)

• Systolic pulmonary arterial pressure >35 to 40 mm Hg
• Mean pulmonary arterial pressure ≥25 mm Hg
• PCWP, LAP, LVEDP <15 mm Hg
• Pulmonary vascular resistance >3U
Pathophysiology of PAH: An Integrated View

Genetic Predisposition

Other Risk Factors

Altered Pathways and Mediators

Proliferation

Thrombosis

Vasoconstriction

Vascular Remodeling
Mechanisms of Disease Pathology

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
     - ↓ Nitric oxide synthase
     - ↓ Prostacyclin production
     - ↑ Thromboxane production
     - ↑ Endothelin 1 production
   - Vascular Smooth Muscle Dysfunction
     - Impaired voltage-gated potassium channel (K\textsubscript{V1.5})

3. Disease Progression
   - Loss of response to short-acting vasodilator trial

Susceptibility
   - Abnormal BMPR2 gene
   - Other genetic factors

Normal

Reversible Disease

Irreversible Disease
Mediators and Pathways in PAH

<table>
<thead>
<tr>
<th>Increased Activity</th>
<th>Reduced Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelin-1</td>
<td>Prostacyclin</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Prostacyclin synthase</td>
</tr>
<tr>
<td>Thromboxane A₂</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>Angiopoietin-1</td>
<td>Nitric oxide synthase</td>
</tr>
<tr>
<td>PAI-1</td>
<td>VIP</td>
</tr>
<tr>
<td>Growth factors</td>
<td>Kᵥ channel</td>
</tr>
<tr>
<td>Oxidant stress</td>
<td>Fibrinolysis</td>
</tr>
<tr>
<td>Inflammation</td>
<td></td>
</tr>
</tbody>
</table>

PAI = plasminogen activator; VIP = vasoactive intestinal peptide.
Lung/Respiratory Diseases Associated with PH

<table>
<thead>
<tr>
<th>Obstructive Lung Diseases</th>
<th>Restrictive Lung Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>• COPD*</td>
<td>• Neuromuscular diseases</td>
</tr>
<tr>
<td>• Asthma</td>
<td>• Kyphoscoliosis*</td>
</tr>
<tr>
<td>• Cystic fibrosis</td>
<td>• Thoracoplasty</td>
</tr>
<tr>
<td>• Bronchiectasis</td>
<td>• Sequelae of pulmonary tuberculosis</td>
</tr>
<tr>
<td></td>
<td>• Sarcoidosis</td>
</tr>
<tr>
<td></td>
<td>• Pneumoconiosis</td>
</tr>
<tr>
<td>Respiratory Insufficiency of “Central” Origin</td>
<td>• Drug-related lung diseases</td>
</tr>
<tr>
<td>• Central alveolar hypoventilation</td>
<td>• Extrinsic allergic alveolitis</td>
</tr>
<tr>
<td>• Obesity-hypoventilation syndrome*</td>
<td>• Connective tissue diseases</td>
</tr>
<tr>
<td>• Sleep apnea syndrome*</td>
<td>• Idiopathic interstitial pulmonary fibrosis*</td>
</tr>
<tr>
<td></td>
<td>• Interstitial pulmonary fibrosis of known origin</td>
</tr>
</tbody>
</table>
Lung/Respiratory Diseases Associated with PH

Silicosis

Fibrosis
BREATHE-5: Trial Design

- Randomized, double-blind, placebo-controlled trial of Bosentan in Eisenmenger’s Syndrome

- N=52

- Duration: 4 months

- Participating Centers
  - USA (TCH/BCM-Houston, Boston)
  - Europe (Scotland, England, Italy, Belgium)
  - Australia

*Circulation 2006*
BREATHE-5 Summary

In the 1st ever randomized, placebo-controlled study of Eisenmenger’s patients, Tracleer:

- Does not reduce systemic oxygen saturation
- Significantly reduces PVRi
- Significantly improves exercise capacity (6MWD)
- Safety profile consistent with previous prospective clinical trials

Circulation 2006
Adult Congenital Heart Cases

(Challenging cases...)

[Image of a large adult and a small child]
Adult Congenital Heart Cases: Case #1

• 35 y/o woman

• Prior hx of partial AV canal, status-post cath and repair at 1.5 years old

• Normal childhood and young adulthood

• Fam Hx: Married, one adopted child
  – Brother has VSD, others have Musc Dystrophy

• Returns now with sx of worsening dyspnea of exertion and lower extremity edema
ACHD Case #1

• Physical Exam
  – 5’5” 98kg, BP 134/84     Pulse ox=93% on RA
  – No clubbing
  – Chest: bilat transverse thoractomy scars
  – RRR, loud P2, III/VI HSM at LLSB→axilla
  – Lungs clear
  – No ascites
  – Bilat 1+ pitting edema
ACHD Case #1
Echo: ASH 2.5mm, mild SAM
TR jet 4.8 m/s = PASP 92 mmHg + RAP
ACHD Case #1

• V/Q Scan: no unmatched defect

• CT Scan: dilated branch pulm arteries, but no parenchymal lung disease or emboli

• 6 Minute Walk: 339 m
ACHD Case #1: PFTs

- Normal TLC
- Normal spirometry
- Mildly reduced DLCO

- NEXT: Cardiac Cath…
ACHD Case #1

• QUESTIONS:
  – Is this primary PAH?
  – Is this secondary PAH (due to MR and complicated by obesity/sleep apnea)?
  – What is best management option?
    • Medical (pharmacologic tx) or surgical MVR?
ACHD Case #1: Follow-up

• Started on Macitentan 10 mg QD
  – 2 forms of birth control
  – Monthly LFTs and pregnancy tests
• Patient lost weight (from 98kg to 87 kg)
• CPAP use

• *Now, feels “much better”*

• Echo: TR jet=3.5 m/s $\rightarrow$ PASP=49mmHg + RAP
• 6MW: 380 m

• SENT FOR MV Repair…
Post-op: MV much improved!
Post MV Repair: TR jet
ACHD Case #2

- 35 y/o woman
- Murmur heard at age 11 y/o
- Diagnosed with single ventricle, large VSD
- Cath’ ed at age 11 y/o in Iowa
  - Single LV, L-TGA, VSD, elevated PAP
  - Told “nothing can be done”
- Moved to Minnesota, cath’ ed again at age 23
  - Pulm HTN with systemic PAP
  - Told “nothing can be done, get a heart-lung transplant”
- Moved to Austin at age 33
  - Came for consult in Houston…
  - Dx=DILV, small RV, L-TGA, large VSD, Pulm HTN
BSA 1.79 m²
HGB 18.4 mg/dL
EST O₂ 221.96 mL
Qp : Qs 0.85 : 1
CO Fick 6.9 L/min
CI 3.85 L/min/m²
### 35 y/o with large VSD and PAH

<table>
<thead>
<tr>
<th></th>
<th>21% FIO2</th>
<th>100% FIO2</th>
<th>100% FIO2 Adenosine</th>
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<tbody>
<tr>
<td>Qp:Qs</td>
<td>0.85:1</td>
<td>3.6:1</td>
<td>8.5:1</td>
</tr>
<tr>
<td>Qs (Fick)</td>
<td>6.9</td>
<td>4.2</td>
<td>4.6</td>
</tr>
<tr>
<td>FA Sat</td>
<td>87%</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>RPA Systolic Pressure</td>
<td>123</td>
<td>103</td>
<td>93</td>
</tr>
<tr>
<td>Mean PAP</td>
<td>88</td>
<td>85</td>
<td>81</td>
</tr>
<tr>
<td>PVR (W-U)</td>
<td>9.7</td>
<td>4.3</td>
<td>1.3</td>
</tr>
<tr>
<td>PCWP</td>
<td>31</td>
<td>38</td>
<td>42</td>
</tr>
<tr>
<td>RV:FA (mmHg)</td>
<td>0.97</td>
<td>0.72</td>
<td>0.66</td>
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Case #3: Chronic Pulm HTN

• 50 year old man, worsening DOE and exertional cyanosis

• S/p atrial septal defect (ASD) closure in 1977 (Bombay, India) at age 17 y/o
  – He “had Pulm HTN” at surgery in 1977
  – Seen by local cardiologist in 1998: PAH confirmed, and pt sent to PAH specialist
    • Macitentan and then Sildenafil started

• Pt is also overweight (BMI=29) and has sleep apnea
Chronic PAH case
Case #3: Chronic Pulm HTN

• Jan 2011: RHC by Pulm MD
  – Qs (Fick) = 8.1 L/min
  – Oxygen “step-up” noted in the RPA
  – Qp:Qs = 1.5:1 (L to R shunt!!!)
  – PVR = 5.0 Wood Units

• Sent for a cardiac MRI…
  – *sinus venosus ASD*
  – IVC enters at LA/RA junction
Cardiac Magnetic Resonance
Cardiac Magnetic Resonance
Transesophageal Echo (example)
TCH MRN 3000846173

Wt = 68 kg  BSA = 1.8m²
Hb = 14 g/dL
MD = W. Franklin

Qp : Qs = 1.1 : 1
PVR = 4.9 W.U

Qₜ (Fick): 7.2 L/min

All data are on room air, not intubated.
Sinus Venosus ASD test occlusion to stop inter-atrial shunt
# ASD Test Occlusion in the Cath Lab

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<thead>
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<th></th>
<th>Baseline</th>
<th>Balloon Up</th>
<th>Balloon Up + Exercise (15min)</th>
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<tbody>
<tr>
<td><strong>Qs (L/min)</strong></td>
<td>7.2</td>
<td>7.2</td>
<td>7.4</td>
</tr>
<tr>
<td><strong>Qp:Qs</strong></td>
<td>1.1</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>PVR</strong></td>
<td>5</td>
<td>6.7 (est’d)</td>
<td></td>
</tr>
<tr>
<td><strong>RVSP</strong></td>
<td>86</td>
<td>76</td>
<td>102</td>
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<tr>
<td><strong>RFA mmHg</strong></td>
<td>122</td>
<td>132</td>
<td>155</td>
</tr>
<tr>
<td><strong>RV:RFA</strong></td>
<td>0.7:1</td>
<td>0.57:1</td>
<td>0.68:1</td>
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<tr>
<td><strong>RAP</strong></td>
<td>9</td>
<td></td>
<td>SVC=11</td>
</tr>
<tr>
<td><strong>PCWP</strong></td>
<td>13</td>
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<tr>
<td><strong>LVEDP</strong></td>
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THANK Y’ALL!!!
QUESTIONS?

My Doctor said "Only 1 glass of alcohol a day". I can live with that.