Effectively treating patients with pulmonary hypertension:

*The next chapter*

Stuart Rich, M.D.

*Professor of Medicine*
*University of Chicago*

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**The Right Ventricle Determines Survival in Pulmonary Hypertension**

- Baseline variables
  - Functional class
  - Exercise capacity
  - Right atrial pressure
  - Cardiac output
  - RVEF

- Variables in treated patients
  - Functional class
  - Right atrial pressure
  - RVEF

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**Lowering PAP will improve RV function in PH**

- Lung transplantation

- Pulmonary thromboendarterectomy for CTEPH
Single-Lung Transplantation for Pulmonary Hypertension
Three-Month Hemodynamic Follow-up

Lowering PAP will improve RV function in PH
- Lung transplantation
- Pulmonary endarterectomy for CTEPH

Chronic Thromboembolic Pulmonary Hypertension:
Pre- and Postoperative Assessment with MR Imaging

Approved Pulmonary Vasodilators
Do Not Restore Normal PAP


Randomized controlled trials
There is a general misunderstanding of the underlying causes of PAH

- PAH is NOT caused by...
  - Over expression of endothelin
  - Inadequate production of nitric oxide
  - Inability to produce endogenous prostacyclin

Survival in patients with PPH

*Impact of the current treatment era*

<table>
<thead>
<tr>
<th>NIH Registry on PPH</th>
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<tbody>
<tr>
<td>1981-1985</td>
</tr>
<tr>
<td>No approved drugs</td>
</tr>
<tr>
<td>1 yr = 68%</td>
</tr>
<tr>
<td>3 yr = 48%</td>
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</table>

<table>
<thead>
<tr>
<th>French National Registry</th>
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<tbody>
<tr>
<td>2002-2009</td>
</tr>
<tr>
<td>All patients treated with approved drugs</td>
</tr>
<tr>
<td>1 yr = 83%</td>
</tr>
<tr>
<td>3 yr = 58%</td>
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</table>

Survival Rates of Patients With PAH Stratified According to PVR and RVEF at Baseline


Survival in patients with PAH

*Impact of the current treatment era*

- Short term survival in PAH is probably improved
  - Mechanisms are unclear

- Long term survival is marginally better
  - It is possible those with a survival advantage have inherently different right ventricles
The Magic Bullet

Case report

- 53 F presented at age 31 in 1987 with IPAH - non-vasoreactive and was managed conservatively.
- 1991 entered clinical trial of epoprostenol for IPAH which she remained on from that time onward.
- Treated for 18 yrs with no deterioration
- Treadmill test in 2007 she went 13 minutes on a Naughton protocol (7.3 METs)

<table>
<thead>
<tr>
<th>Date</th>
<th>Drug</th>
<th>RA (mmHg)</th>
<th>PAP (mmHg)</th>
<th>CO (L/min)</th>
<th>PVR (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7/87</td>
<td>none</td>
<td>3</td>
<td>74/30</td>
<td>6.24</td>
<td>6.40</td>
</tr>
<tr>
<td>11/91</td>
<td>none</td>
<td>8</td>
<td>128/54</td>
<td>3.40</td>
<td>16.7</td>
</tr>
<tr>
<td>2/92</td>
<td>epo</td>
<td>5</td>
<td>97/34</td>
<td>6.64</td>
<td>9.20</td>
</tr>
<tr>
<td>3/98</td>
<td>epo</td>
<td>6</td>
<td>90/39</td>
<td>6.10</td>
<td>6.90</td>
</tr>
<tr>
<td>2/05</td>
<td>epo</td>
<td>7</td>
<td>95/54</td>
<td>7.60</td>
<td>7.84</td>
</tr>
</tbody>
</table>

Complexity of Pathogenesis of PAH

Case report (cont.)

- July 2009 it was noted that she appeared cachectic with a palpable supraclavicular lymph node.
- Evaluation revealed metastatic adenocarcinoma of the colon.
- Unable to tolerate chemotherapy and died 3 weeks later.
- A post mortem examination was performed.

Pulmonary Vascular Histology

- Extremely advanced end-stage pulmonary vascular disease.
  - Severe medial hypertrophy and intimal proliferation throughout the pulmonary arteriolar bed.
  - Abundant plexiform lesions emblematic of advanced disease.

Severe medial hypertrophy

Widespread Plexiform Lesions
Assessment of the Right Ventricle

- Concentric RVH rather than the eccentric RVH that is typical of PAH.
- Marked RV hypertrophy and hypertrophied myocytes, when compared to the LV.

Implications: Right Ventricle

- It is possible to maintain normal cardiac output for many years in the face of severe pulmonary vascular disease.
  - The fact that the RV had concentric hypertrophy rather than severe dilation may be a key clue to maintaining RV function.
Survival in PAH with Current Treatments

- The underlying disease will progress regardless of the treatment used
- Patient survival is linked to how the RV adapts
  - Some patients adapt well
  - Some patients adapt poorly

RV Dysfunction in Pulmonary Hypertension

RV failure is a consequence of a maladaptive response to chronic pressure overload

Determinants of RV Work in Pulmonary Hypertension

- RV volumes may increase as much at 3 times
- RV systolic pressure may increase as much as 5 times
- RV work may increase as much as 15 times normal
- Right ventricular myocardial oxygen supply has little ability to increase

Aortic Pressure and Coronary Blood Flow
Pulmonary hypertension and coronary artery driving pressure

Hemodynamic and biochemical correlates of RV failure from pulmonary hypertension

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>RV Hypertension</th>
<th>Failure</th>
<th>Phenylephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary driving pressure (mmHg)</td>
<td>65</td>
<td>44</td>
<td>23</td>
<td>78</td>
</tr>
<tr>
<td>Lactate/pyruvate</td>
<td>17.6</td>
<td>13.9</td>
<td>56.8</td>
<td>19.5</td>
</tr>
</tbody>
</table>


The Downward Spiral

Hypotension  \( \uparrow \) RVEDP  
Reduced RV Coronary Blood Flow  
RV Ischemia  
Cardiac Output
The relationship between right coronary pressure and right ventricular segment shortening for conscious and anesthetized states

Consequence of pulmonary hypertension on RV myocardial perfusion

- Myocardial perfusion goes from being both systolic and diastolic to diastolic only.
- The RV hypertrophies, but coronary blood supply remains unchanged.
- RV work is dramatically increased without a compensatory increase in coronary blood flow.
- Tachycardia makes everything worse.

It may be more than just reduced coronary artery flow

Reduced Capillary Density in an Animal Model of Pulmonary Arterial Hypertension

*Circulation. 2009:120:1951-1960*
Capillary Rarefaction in Scleroderma PAH

Archer-unpublished

RV

LV

Human Tissue Array

Glut1 in the RV in scleroderma

Fluorodeoxyglucose PET images of a patient with mild (A, mean pulmonary artery pressure, 33 mm Hg) and severe pulmonary hypertension (B, mean pulmonary artery pressure, 81 mm Hg)

Fluorodeoxyglucose PET images of a patient with mild (A, mean pulmonary artery pressure, 33 mm Hg) and severe pulmonary hypertension (B, mean pulmonary artery pressure, 81 mm Hg)

Fluorodeoxyglucose PET images of a patient with mild (A, mean pulmonary artery pressure, 33 mm Hg) and severe pulmonary hypertension (B, mean pulmonary artery pressure, 81 mm Hg)

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Glycolytic Metabolism of the RV in a Patient with Pulmonary Hypertension

RV failure in PH is the combined result of an inadequate response to excessive demands affected by:

- Reduced coronary artery blood flow
- Reduced capillary density
- Metabolic shift to glycolytic metabolism
Potential strategies to preserve RV function in PAH

- If we believe that similarities exist between chronic left heart failure and chronic right heart failure, then we should consider:
  - Chronic inotropic infusion therapy
  - Beta blockade
  - Surgical interventions

Lessons from the Left

- Chronic inotropic infusion therapy

Existing PAH therapies

- Parenteral prostacyclins
  - Work by raising cardiac output (similar to inotropes)
  - Do not appear to have long term toxic effects

- PDE-5 inhibitors
  - Improve RV contractility
  - Dose response increase in cardiac output
Effects of prostacyclin on the pulmonary vascular tone and cardiac contractility of patients with secondary to end-stage heart failure

...PGI2 produced a significant positive inotropic effect (contractile element maximum velocity increased from 1.10 ± 0.09 to 1.33 ± 0.13 circ/s, p <0.009)...

The American Journal of Cardiology
Volume 82; 1998: Pages 749-755

Phosphodiesterase Type 5 Is Highly Expressed in the Hypertrophied Human Right Ventricle, and Acute Inhibition of Phosphodiesterase Type 5 Improves Contractility

...Mean data showing that the PDE5 inhibitor MY5445 increased contractile pressure and both maximum and minimum dP/dt in a dose-dependent manner in the RVH but not the normal RV ...

Circulation. 2007;116:238-248

Potential strategies to preserve RV function in PAH

Lessons from the Left

- Chronic inotropic infusion therapy
  - Will require RCT
  - Do we need it?
- Beta blockade

Beta Blockade Reverses Right Heart Remodeling in Pulmonary Hypertensive Rats

ajrccm 2010;182:652
Potential strategies to preserve RV function in PAH

*Lessons from the Left*

- Chronic inotropic infusion therapy
- Beta blockade
  - Very difficult to initiate given the current guidelines
- Surgical interventions

An Inter-Atrial Shunt May be of Benefit

- Clinical evidence:
- Patients with PPH + PFO live longer than those without shunting (Rozkovec 1986; Glanville 1987)

<table>
<thead>
<tr>
<th></th>
<th>Survival</th>
<th>p value</th>
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<tbody>
<tr>
<td>Family Disease</td>
<td>(&lt;5 \text{ years (n = 10)}) (&gt;5 \text{ years (n = 16)})</td>
<td>NS</td>
</tr>
<tr>
<td>HT</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Hx Pregnancy</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>PFO</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>RHF any stage</td>
<td>18</td>
<td>40</td>
</tr>
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Survival is better in Eisenmenger syndrome than in IPAH

Atrial septostomy

*Rationale*

- Deterioration in symptoms and death in idiopathic PAH are associated with reduced systemic flow and dilation and failure of the RV
- An ASD would allow:
  - R-to-L shunt to increase systemic output
  - Decompression of the RV alleviating its failure
Atrial Septostomy as Palliative Therapy for Refractory Primary Pulmonary Hypertension


- Age = 27.7 ± 17 years
- 70% females
- NYHA Class: 3.6 ± 0.4
  - 33 (14.8%) procedure-related deaths
  - 163/186 (87.6%) improved
  - 23 (12.4%) not-improved

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>After</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRAP, mmHg</td>
<td>14.6 ± 8.0</td>
<td>11.6 ± 6.3</td>
<td>0.000</td>
</tr>
<tr>
<td>mLAP, mmHg</td>
<td>5.7 ± 3.3</td>
<td>8.1 ± 4.0</td>
<td>0.000</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>2.04 ± 0.69</td>
<td>2.62 ± 0.84</td>
<td>0.000</td>
</tr>
<tr>
<td>SaO₂ %</td>
<td>93.3 ± 4.1</td>
<td>83.0 ± 8.5</td>
<td>0.000</td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>64.3 ± 17.6</td>
<td>65.7 ± 18.3</td>
<td>0.169</td>
</tr>
</tbody>
</table>

Acute Hemodynamic Effects After Septostomy

Long-term effects

Graded balloon dilation atrial septostomy in severe primary pulmonary hypertension

A therapeutic alternative for patients nonresponsive to vasodilator treatment

<table>
<thead>
<tr>
<th></th>
<th>1 year Survival</th>
<th>2 year survival</th>
<th>3 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial septostomy</td>
<td>92%</td>
<td>92%</td>
<td>92%</td>
</tr>
<tr>
<td>Historical Controls</td>
<td>73%</td>
<td>59%</td>
<td>52%</td>
</tr>
<tr>
<td>NIH Registry</td>
<td>61%</td>
<td>49%</td>
<td>38%</td>
</tr>
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</table>


Atrial Septostomy in PAH: Indications

- Palliative. When no other options were available
- Rescue of patients with Syncope / RHF despite maximal therapy (IV Prostacyclin)
- As a bridge to transplantation

Atrial Septostomy in PAH: Contraindications

- Right atrial pressure must be less than 20 mmHg
- Systemic arterial oxygen saturation must be greater than 90% at rest

Atrial septostomy has been criticized as a therapeutic intervention because it does not protect the pulmonary vasculature from developing advanced disease, but neither do the approved medical therapies.

PAH Treatment Algorithm

2008 US Organ and Tissue Transplant Survival and Cost Estimates

- Double Lung Transplantation
  - Number = 764
  - Charges = $657,800 (180 days)
  - Hospital length of stay = 30 days
  - Survival
    - 1 yr = 78%
    - 3 yr = 59%
    - 5 yr = 45%

Primary Pulmonary Hypertension
Waiting List Patient Characteristics at End of Year
Active Waitlist Patients, 2007

<table>
<thead>
<tr>
<th>Waiting List Duration</th>
<th>0-30 days</th>
<th>30-60 days</th>
<th>60-90 days</th>
<th>3-6 months</th>
<th>6-12 months</th>
<th>1-2 years</th>
<th>2+ years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage</td>
<td>9%</td>
<td>9%</td>
<td>7.5%</td>
<td>19%</td>
<td>18%</td>
<td>17%</td>
<td>21%</td>
</tr>
</tbody>
</table>

Source: OPTN/SRTR Data as of May 1, 2008

Potential strategies to preserve RV function in PAH
Lessons from the Left

- Chronic inotropic infusion therapy
  - Will require RCT
- Beta blockade
  - Very difficult to initiate given the current guidelines
- Surgical Interventions
- Mechanical support (the next chapter)
  - RVAD

Schematic representation showing placement of inflow and outflow cannulae for LVADs and RVADs

Krishnamani, R. et al. (2010) Emerging ventricular assist devices for long-term cardiac support
Nat. Rev. Cardiol. doi:10.1038/nrcardio.2009.222
Atrial Septostomy vs. RVAD for PAH

- Both procedures will reduce RA volume/pressure
- Both procedures will increase cardiac index
- The major limitation with atrial septostomy is the fall in arterial oxygen saturation which should not occur with RVAD

Why is a Chronic RVAD likely to be successful as a treatment of PAH?

- Current therapies are associated with poor survival
- Survival is linked to cardiac output
- Experience (septostomy) documents improved symptoms and survival with surgical reduction in RAP and increasing cardiac index
- Preliminary experiences with RVADs are favorable
It may be the next chapter…

…but it won't be the last one.