Seeing pulmonary hypertension from your and your patient’s perspective

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University of Minnesota
Disclosures

• My salary is indirectly paid by Fairview and is production based – however RVU targets are so high I could never come close to incentive compensation.

• Two of my graduate students formed a company to produce the first mechanical device for treating PH and have received $6 million for developing “disruptive” technology. I have no financial interest (damn it). The University of Minnesota has a royalty position and “encourages” me to provide unreimbursed advice.

• My car and my suit are 11 years old. The dog ate dry dog food.

• I receive no industry compensation.

• I will identify and discuss off-label and research findings.

• My research is supported by generous grants from the Lillihei Foundation as well as from the Pritzker and Stowell families.
Echo reports suggest PH is present. Pulmonary hypertension is a progressive disease that worsens as time advance, quickly or slowly depending on the patient and characteristics of the disease. There is currently no cure for the disease, but treatments exist to help ease symptoms and prolong lifespan. When untreated PH patients face a poor prognosis estimated at 2.8 years. The probability of survival for untreated patients is 68% one year after the onset of the disease which drops to 48% after three years and to 34% after five years.
Shining the light on the individual patient with PH
Pulmonary Hypertension: Define Lesion

Post-Capillary PH
(PCWP > 15 mmHg; PVR nl)

PAH
Respiratory Diseases
PE

Atrial Myxoma
Cor Triatriatum

MV Disease

Pre-capillary PH
PCWP < 15 mmHg
PVR > 3 Wu

Mixed PH

PV compression
PVOD

Myocardial Disease
Dilated CMP-ischemic/non-isc.
Hypertrophic CMP
Restrictive/infiltrative CMP
Obesity and others

Systemic HTN
AoV Disease
Diagnosis

PEDIATRIC EMERGENCY CARE

FOR THE FOLLOWING INJURIES:
- WENT OUTSIDE IN COLD WEATHER WITH WET HAIR
- PETTED STRANGE DOG
- ATE ICE CREAM TOO FAST AND GOT HEADACHE
- CROSSED EYES AND GOT THEM STICK
- RAN WITH SCISSORS
- WENT SWIMMING LESS THAN 12 HOUR AFTER EATING
- TALKED ON PHONE DURING THUNDERSTORM
- CRACKED KNOCKLES TO MUCH
- PEB BURNS
- ALL OTHER INJURIES

Room 107
Room 111
Room 110
Room 113
Room 109
Room 114
Room 117
Room 118
Room 120
Room 125

Shortness of Breath Clinic

Out of shape
Asthma
COLD
Heart
PE
PAH
Echo versus catheterization

PA Pressure

Echo vs Catheterization

![Graph showing PA Pressure comparison between Echo and Catheterization for All and IPAH cases.](image)
Accuracy of PH Diagnosis by Echocardiography in Advanced Lung Disease

- Cohort study of 374 lung transplant patients
- All patients had Doppler echo 24–48 h prior to RHC
- Prevalence of PH: 25%
- Echo frequently inaccurate leading to over diagnosis of PH in patients with advanced lung disease

Arcasoy SM et al. Am J Respir Crit
Echo: fellow travelers of PH or not

- Pericardial effusion
- RA size
- Inter-ventricular position
- Right ventricular hypertrophy
- PA acceleration time
- Congenital heart disease
- Bubble shunt
- TAPSE
Clinical Classification

PAH
- Idiopathic PAH
- Heritable
- Drug and toxin
- CTD
- HIV
- Liver
- Schistosomiasis
- Chronic hemolytic

PH left heart disease
- Systolic dysfunction
- Diastolic dysfunction
- Valvular heart disease

Pulmonary disease
- COLD
- ILD
- Mixed obstructive/restrictive
- OSA
- Alveolar hypoventilation
- Altitude habituation

Chronic Thromboembolic

Mixed bag
- Splenectomy
- Myeloproliferative
- Thyroid disorders
When a subject is highly controversial... one cannot hope to tell the truth. One can only show how one came to hold whatever opinion one does hold. One can only give one's audience the chance of drawing their own conclusions as they observe the limitations, the prejudices, the idiosyncrasies of the speaker.

(Virginia Woolf)
To Bayesian or not to Bayesian – that is the question
There is a 20+% chance the echo is wrong and the patient does not have PH.

PH represents a spectrum of diseases that have vastly different treatments.

SG complication rate low
- Serious adverse events 76 (1.1%)
- Deaths 4 (0.055%)

In order to secure PAH treatments must have hemodynamic data for insurance coverage.

To the PH prima-donallas their only tool is a Swan Ganz hammer, and every patient is a nail.
Outcomes from RHC

- Normal – no pulmonary hypertension of any type
- Pulmonary venous hypertension – HFrEF, HFpEF, high flow
- Pre-capillary pulmonary hypertension
- Mixed or disproportionate

The latter three all have therapeutic and prognostic significance
Current survival statistics generally represent mono-therapy.

Multi-drug therapy is way to go but data just emerging.

Survival is better than historical controls but general care is better.

Careful collaboration with primary care.

Landmark driven therapeutic decisions – 6 minute walk, cardiac output, pulmonary compliance vs. resistance.
Year Overall Survival
There was no significant difference in survival among patients with PH who were studied. $p_1$ = p value for typical IPAH versus atypical IPAH; $p_2$ = p value for typical IPAH versus PH-HFpEF; $p_3$ = p value for atypical IPAH versus PH-HFpEF; other abbreviations as in Figure 1.
Therapeutic decision making in PH

Double double toil and trouble

Fire burn and cauldron bubble

Eye of newt and toe of frog

Wool of bat and tongue of dog…

*Macbeth*
A promising treatment is the larval stage of a disappointing one.
Limitations to drawing conclusions

• “SNAFU” small numbers adequate follow-up
  – Most studies 12-16 weeks in duration
• No direct, head-to-head comparisons
• *Time to clinical worsening* driven by hospitalizations *not* mortality or therapy switch
Ambition: combination vs. monotherapy

First occurrence of a composite end point of death, hospitalization for worsening pulmonary arterial hypertension, disease progression, or unsatisfactory long-term clinical response
<table>
<thead>
<tr>
<th>End Point</th>
<th>Combination-Therapy Group (N=253)</th>
<th>Pooled-Monotherapy Group (N=247)</th>
<th>Ambrisentan-Monotherapy Group (N=126)</th>
<th>Tadalafil-Monotherapy Group (N=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end point</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First event of clinical failure — no. of participants (%)</td>
<td>46 (18)</td>
<td>77 (31)</td>
<td>43 (34)</td>
<td>34 (28)</td>
</tr>
<tr>
<td>Death</td>
<td>9 (4)</td>
<td>8 (3)</td>
<td>2 (2)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Hospitalization for worsening pulmonary arterial hypertension</td>
<td>10 (4)</td>
<td>30 (12)</td>
<td>18 (14)</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>10 (4)</td>
<td>16 (6)</td>
<td>12 (10)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Unsatisfactory long-term clinical response</td>
<td>17 (7)</td>
<td>23 (9)</td>
<td>11 (9)</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Hazard ratio, combination therapy vs. monotherapy (95% CI)</td>
<td>Reference</td>
<td>0.50</td>
<td>0.48</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>(0.35 to 0.72)</td>
<td>(0.31 to 0.72)</td>
<td>(0.34 to 0.83)</td>
<td></td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>—</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP level†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage change in geometric mean from baseline to week 24</td>
<td>-67.2</td>
<td>-50.4</td>
<td>-56.2</td>
<td>-43.8</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>Reference</td>
<td>&lt;0.001</td>
<td>0.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Satisfactory clinical response at week 24 — no. of participants/total no. (%)‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>91/234 (39)</td>
<td>66/226 (29)</td>
<td>35/113 (31)</td>
<td>31/113 (27)</td>
</tr>
<tr>
<td>No</td>
<td>143/234 (61)</td>
<td>160/226 (71)</td>
<td>78/113 (69)</td>
<td>82/113 (73)</td>
</tr>
<tr>
<td>Unknown</td>
<td>19/253 (8)</td>
<td>21/247 (9)</td>
<td>13/126 (10)</td>
<td>8/121 (7)</td>
</tr>
<tr>
<td>Odds ratio, combination therapy vs. monotherapy (95% CI)</td>
<td>Reference</td>
<td>1.56</td>
<td>1.42</td>
<td>1.72</td>
</tr>
<tr>
<td></td>
<td>(1.05 to 2.32)</td>
<td>(0.88 to 2.31)</td>
<td>(1.05 to 2.83)</td>
<td></td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>—</td>
<td>0.03</td>
<td>0.15</td>
<td>0.03</td>
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</table>
### Ambition

<table>
<thead>
<tr>
<th>6-Minute walk distance — m§</th>
<th>Median (IQR) change from baseline to week 24</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>48.98 (4.63 to 85.75)</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>23.80 (−12.25 to 64.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>27.00 (−14.00 to 63.25)</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>22.70 (−8.25 to 66.00)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change in WHO functional class at week 24</th>
<th>no. of participants/total no. (%)§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>94/252 (37)</td>
</tr>
<tr>
<td></td>
<td>81/244 (33)</td>
</tr>
<tr>
<td></td>
<td>42/124 (34)</td>
</tr>
<tr>
<td></td>
<td>39/120 (33)</td>
</tr>
<tr>
<td>No change</td>
<td>146/252 (58)</td>
</tr>
<tr>
<td></td>
<td>147/244 (60)</td>
</tr>
<tr>
<td></td>
<td>73/124 (59)</td>
</tr>
<tr>
<td></td>
<td>74/120 (62)</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>12/252 (5)</td>
</tr>
<tr>
<td></td>
<td>16/244 (7)</td>
</tr>
<tr>
<td></td>
<td>9/124 (7)</td>
</tr>
<tr>
<td></td>
<td>7/120 (6)</td>
</tr>
<tr>
<td>P value</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>0.36</td>
</tr>
</tbody>
</table>
What do drugs do?

Functional capacity

- Prostanoids
- ERA+PDE V
- ERA
- 81.8%
- 28.3%
- 25.2%

Time to clinical worsening

- Riociguat
- ERA+PDE V
- PDE V
- ERA
- 2.8%
- 3.9%
- 5.7%
- 7.7%

Comparative Effectiveness of Pharmacological Interventions for Pulmonary Arterial Hypertension: A Systematic Review and Network Meta-Analysis

31 RCTs, including 6,565 patients with PAH
Diseases desperate grown are rescued by desperate measures or not at all
How many drugs does it take?

Nature is devishly clever and redundancy abounds. It is unreasonable to think that one drug is sufficiently upstream enough to avoid all the alternative pathways and not have limiting off-target effects. The treatment of many forms of malignancy did not become reasonably effective until multiple drugs were utilized.
Nursing is a very demanding profession. To start with, nurses must learn everything a doctor learns, so that whenever a situation arises that might develop into a mistake on the part of the doctor if the nurse did what the doctor ordered instead of what he meant to do, the nurse can distinguish the latter from the former and prevent the mistake from occurring. Then nurses must learn how to use this knowledge so that neither the doctor nor the patient is aware they possess it, for in the former instance, it might cause the patient to lose confidence in the doctor, and in the latter, it might cause the doctor to lose confidence in himself. Finally, if, despite a nurse’s best efforts, things are not going well between doctor and patient, and the nurse can’t patch it up, the nurse must take the blame.
Figure 2. Pulmonary artery denervation circular catheter and the target location, indicated by red arrows.

Scheme of the pathophysiological concept of chronic thromboembolic pulmonary hypertension.

- **VTE**
  - **Acute PE**
    - Incomplete resolution and organisation of thrombus
      - Lack of thrombus angiogenesis
        - Development of fibrotic stenoses/occlusions
          - Adaptive vascular remodelling of resistance vessels

Factors:
- Infection and inflammation
- Immunity
- Genetics
Figure 1. Examples of vascular reconstruction for 2 control subjects (top) and 2 patients with chronic thromboembolic pulmonary hypertension (bottom). Some patients exhibited patchy disease (bottom left), whereas others exhibited diffuse disease throughout the vascular tree (bottom right).


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Biological tissues exist in such a state of offsetting forces.

The most familiar example is the balance between blood pressure and the elastic tension in the cardiovascular system that contains and conveys blood without bursting or collapsing.
Drugs for PAH cannot do this consistently either.
TWO DRUG THERAPY WITH PDE V INHIBITION AND AMBRISENTAN IMPROVES PULMONARY ARTERY COMPLIANCE

Patarroyo M.\(^1\), Sharma A.\(^2\), Gillies H.C.\(^3\), Blair C.\(^3\), Shao Y.\(^3\), Pritzker M.\(^2\)

\(^1\)Allegheny General Hospital-Pittsburgh, \(^2\)University of Minnesota-Minnesota, \(^3\)Gilead Sciences Inc-Foster City, CA/US on behalf of the ATHENA-1 Study Investigators.
Bench: Hemodynamic Benefits

Pressure in Pulmonary Artery

- **Device**
  - Compliance increased by 0.51 ml/mmHg (in this example)

- **Hemodynamic Effects**
  - Lower systolic pressure
    - reduces RV work & wall stress
    - increases SV
  - Higher diastolic pressure
    - increases blood flow
  - Reduction of pulse pressure
    - breaks the disease-stimulating feedback loop

- **Expected Patient Effects**
  - Increase in exercise capacity & QOL
  - Decrease in mortality likely
Efficacy in Animals

- Calves raised at altitude develop PAH similar to the human form
- Early study shows significant increase in cardiac output

![Graph of Calf Cardiac Output](image)

![Graph of Right Ventricular PV loop](image)
Angiopoietin alveolar capillary membrane