Surgeon-Scientist: Standing on the Shoulders of Giants

J. Hunter Mehaffey MD, MSc
If I have seen further it is by standing on the shoulders of Giants.

- Isaac Newton in 1675
“We [the Moderns] are like dwarves perched on the shoulders of giants [the Ancients], and thus we are able to see more and farther than the latter. And this is not at all because of the acuteness of our sight or the stature of our body, but because we are carried aloft and elevated by the magnitude of the giants.”

- Bernard of Chartres 12th Century
Nobel Laureate Surgeons

1. Theodor Kocher, 1909, Physiology, Pathology, and Surgery of the Thyroid
2. *Allvar Gullstrand, 1911, Dioptrics of the Eye
3. Alexis Carrel, 1912, Anastomosis of Vessels and Transplantation of Organs
4. Robert Barany, 1914, Vestibular System
5. Frederick Banting, 1923, Discovery of Insulin
7. Werner Forssmann, 1956, Cardiac Catheterization
Alexis Carrel
Frederick Banting
.... if the science of surgery, then, requires genius, knowledge, and indefatigable application to render its professors truly respectable, what must we think of the insolence . . . of those who represent it as a low mechanical art which may be taught a butcher’s boy in a fortnight. . . .

- John Jones (Surgeon US Army 1769)
(Father of American Surgery and Author of America's First Medical Book)
John Gibbon
Irv Kron
Adenosine 2A Receptor
**Methods**

- Sternotomy (n=15 pigs)
- Electric Ventricular Fibrillation Arrest: 9V Battery
- Randomized on Induction of ECMO (n=5 each)
  - Vehicle Control
  - Low Dose ATL1223 (0.3ng/kg/min)
  - High Dose ATL1223 (0.6ng/kg/min)
Systemic Injury
Fluid and Hemodynamics

A.

Fluid (mL):
- DMSO Control
- Low-dose ATL1223
- High-dose ATL1223

B.

Urine Output (mL):
- DMSO Control
- Low-dose ATL1223
- High-dose ATL1223

C.

Final Flow (L/min):
- DMSO Control
- Low-dose ATL1223
- High-dose ATL1223

D.

Total Epinephrine (mg):
- DMSO Control
- Low-dose ATL1223
- High-dose ATL1223

p-values:
- Fluid: p=0.06
- Urine Output: p=0.10
- Final Flow: p=0.001
- Total Epinephrine: p=0.17
Plasma Cytokines

Proinflammatory Cytokines

A. TNF-α (ng/mL)

- DMSO Control
- Low-dose ATL1223
- High-dose ATL1223

Hours

B. IFN-γ (ng/mL)

- DMSO Control
- Low-dose ATL1223
- High-dose ATL1223

Hours

Anti-inflammatory Cytokines

A. IL-4 (ng/mL)

- DMSO Control
- Low-dose ATL1223
- High-dose ATL1223

Hours

B. IL-10 (ng/mL)

- DMSO Control
- Low-dose ATL1223
- High-dose ATL1223

Hours
Organ Injury

A.

- DMSO Control
- Low-dose ATL1223
- High-dose ATL1223

NGAL (mg/mL) vs. Hours

B.

- DMSO Control (m=4.4)
- Low-dose ATL1223 (m=3.8)
- High-dose ATL1223 (m=2.5)
- Linear Regression

Troponin (ng/mL) vs. Hours

*p=0.01*
Meaningful bench research begins at the bedside and must be translated back to the bedside.

- Irv Kron
Ex Vivo Lung Perfusion
Rehabilitation on EVLP

- **PO$_2$/FiO$_2$ Ratio**:
  - Duration of EVLP (hours): 1, 4
  - Comparison: 1 hour vs. 4 hours, $p=0.02$

- **Dynamic Compliance (mL/cm H$_2$O)**:
  - Duration of EVLP (hours): 1, 4
  - Comparison: 1 hour vs. 4 hours, $p=0.02$

- **Wet / Dry Ratio**:
  - In Vivo Control, Ex Vivo Control, EVLP
  - Comparison: In Vivo Control vs. Ex Vivo Control, $p=0.002$
  - In Vivo Control vs. EVLP, $p=0.03$

- **Lung Injury Severity Scores**:
  - In Vivo Control, Ex Vivo Control, EVLP
  - Comparison: In Vivo Control vs. Ex Vivo Control, $p=0.01$
  - In Vivo Control vs. EVLP, $p=0.03$
In Vivo Lung Perfusion
Methods

Injury
- 8 pigs
- 50 ul/kg Intravenous LPS
- Central ECMO Cannulation

Right Lung
- Systemic Circulation
- Standardized ECMO

Left Lung (IVLP)
- Steen Solution
- Flow 8% Cardiac Output

Reperfusion
- IVLP Decannulation
- Hourly ABG/Compliance
- Wean ECMO
- Tissue Sample

2 Hours

4 Hours

4 Hours
Superior Function

The graph illustrates changes in various oxygenation parameters over time. Key observations include:

- **PO$_2$/Fi$_O$2 Ratio (mmHg):**
  - Injury phase shows a sharp decline.
  - IVLP phase exhibits some fluctuations.
  - Reperfusion phase has a gradual improvement.

- **Systemic Oxygenation:** Demonstrates an initial drop followed by a gradual increase.

- **Left Lung Oxygenation:** Shows significant fluctuations across the timeline.

- **Right Lung Oxygenation:** Remains relatively stable.

- **Total Lung Compliance:** Reflects changes in lung mechanics, with notable variability during IVLP.

- Total Lung Compliance is marked by *p<0.05* indicating statistical significance.

The graph highlights the impact of injury, IVLP, and reperfusion on lung oxygenation and compliance, emphasizing the dynamic nature of these physiological responses.
Reduced Histologic Injury / Edema

Right Lung

Left Lung

Wet / Dry Weight Ratio

\[ p = 0.01 \]
Cytokines

**Tissue**

- A. Tissue pg/mL INF-γ, Right Lung vs. Left Lung, p=0.008
- C. Tissue pg/mL TNF-α, Right Lung vs. Left Lung, p=0.039
- E. Tissue pg/mL IL-4, Right Lung vs. Left Lung, p=0.016

**BAL**

- B. BAL pg/mL INF-γ, Right Lung vs. Left Lung, p=0.047
- D. BAL pg/mL TNF-α, Right Lung vs. Left Lung, p=0.078
- F. BAL pg/mL IL-4, Right Lung vs. Left Lung, p=0.039
Adhesion Molecules

A. Pig 1
   Right  |  Left
---      |---
VCAM-1 (81 kDa)
β-Actin (43 kDa)

B. Pig 1
   Right  |  Left
---      |---
ICAM-1 (57 kDa)
β-Actin (43 kDa)

P = 0.03

P = 0.12
Clinical Translation

- IVLP
  - Right jugular vein
  - Pulmonary vein cannula (transseptal)
  - Pulmonary artery cannula (via right ventricle)

- Ventilator
  - Left jugular vein
  - Pulmonary artery cannula (into left branch)
  - Left superior and inferior pulmonary vein cannulae

- ECMO
It usually requires a considerable time to determine with certainty the virtues of a new method of treatment and usually still longer to ascertain the harmful effects.

Alfred Blalock (1899–1964)
VAD stent
LVAD Limitations
<table>
<thead>
<tr>
<th></th>
<th>Length</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal LV</td>
<td>8.99</td>
<td>120.8 ± 2.2</td>
</tr>
<tr>
<td>Diseased LV</td>
<td>10.77</td>
<td>348.5 ± 3.2</td>
</tr>
</tbody>
</table>
VADstent Porcine Prototype

LV cavity collapse during systole

LV cavity maintained during systole
VADstent Modeling
VADstent Ovine Implant
New ideas seldom have the simplicity of a switched on light bulb.

Thomas Starzl (1926–2017)
Mentors
Colleagues
Questions