Pulmonary Dead Space: Prognosis, Pathogenesis and Significance in ARDS

Michael A. Matthay, MD

Departments of Medicine & Anesthesia
Cardiovascular Research Institute
University of California at San Francisco
Disclosures

Research supported by grants from the NIH Institutes NHLBI and NIAID, and the FDA
- HL51856
- HL51854
- HL11274
- HL110969
- AI 108764

Clinical Trials supported by NIH NHLBI
- HL10871301
- HR56166

GlaxoSmithKline grant -pathogenesis of ARDS from sepsis
Pulmonary Dead Space in ARDS

- Background & rationale
- Primary results plus follow up studies
- Mechanisms
- Estimating and measuring dead space
- Conclusions
• The classic physiologic abnormality in ARDS is hypoxemia

• Secondary to alveolar filling, resulting in low V/Q and intrapulmonary shunting.
Minute ventilation is twice normal in patients with early ARDS. Why?

Either there is a marked increase in carbon dioxide production or there is an increase in alveolar dead space.
Dead space fraction: a measure of wasted ventilation

Comroe, Lung Physiology
Hypotheses

1. The dead space fraction is elevated early in ARDS.

2. An elevated dead space fraction will have an independent predictive value for identifying ARDS patients with a high mortality.
Study Design

- Prospective (1998-2000)
- University Medical Center (UCSF) and City Hospital (SFGH)
- 179 patients with early ARDS
- Clinical, pulmonary, and severity of illness data
Methods

1. Dead space measured with a bedside metabolic monitor (DELTRAC)

2. Dead space fraction = 
   \[
   \frac{(PaCO_2 - PECO_2)}{PaCO_2}
   \]

3. Tidal volume set at 10.0 ± 1.4 ml/Kg/ideal body weight

4. Static respiratory compliance = 
   Tidal volume ÷ (Plateau – end expiratory pressure)
### Characteristics of 179 ARDS Patients

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>48 ± 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical disorder associated with ARDS</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>25%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>31%</td>
</tr>
<tr>
<td>Aspiration</td>
<td>11%</td>
</tr>
<tr>
<td>Major trauma, overdose, other</td>
<td>34%</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>42%</td>
</tr>
</tbody>
</table>
### Baseline Pulmonary Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO$_2$/FiO$_2$</td>
<td>147 ± 61 mmHg</td>
</tr>
<tr>
<td>Tidal Volume</td>
<td>10.0 ± 1.4 (ml/Kg/IBW)</td>
</tr>
<tr>
<td>Respiratory Compliance</td>
<td>30.9 ± 11.1 (ml/cm H$_2$O)</td>
</tr>
<tr>
<td>Minute Ventilation</td>
<td>12.1 ± 4.3 (L/min)</td>
</tr>
<tr>
<td>Dead Space Fraction</td>
<td>0.58 ± 0.10</td>
</tr>
<tr>
<td>Absolute Dead Space</td>
<td>6.5 ± 1.4 (ml/Kg/IBW)</td>
</tr>
</tbody>
</table>
Statistical Analysis

- Primary Outcome Variable = Death before hospital discharge

- Logistic Regression

- SAPS II for severity of illness

- Multiple logistic progression for independent association with death. Each significant variable (<0.05) was introduced into a forward, stepwise, logistic-regression model
### Univariate Variables Associated with an Increased Risk of Death

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors (N = 104)</th>
<th>Nonsurvivors (N = 75)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂/FiO₂</td>
<td>163 ± 63</td>
<td>123 ± 51</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dead Space</td>
<td>0.54 ± 0.09</td>
<td>0.63 ± 0.10</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Resp. CL</td>
<td>33.6 ± 12.0</td>
<td>27.2 ± 8.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LIS</td>
<td>2.2 ± 0.6</td>
<td>2.6 ± 0.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SAPS II</td>
<td>41 ± 15</td>
<td>55 ± 15</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
### Univariate Variables Associated with an Increased Risk of Death

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors (N = 104)</th>
<th>Nonsurvivors (N = 75)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>31%</td>
<td>51%</td>
<td>&lt; 0.008</td>
</tr>
<tr>
<td>Vasopressor</td>
<td>23%</td>
<td>48%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Low TV Protocol (#)</td>
<td>24</td>
<td>7</td>
<td>0.02</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>12</td>
<td>21</td>
<td>0.08</td>
</tr>
<tr>
<td>NPOFC (#)</td>
<td>1.1 ± 1.2</td>
<td>1.5 ± 1.2</td>
<td>0.04</td>
</tr>
</tbody>
</table>
### Variables Independently Associated with an Increased Risk of Death

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead Space Fraction*</td>
<td>1.45 (1.15 - 1.83)</td>
<td>0.002</td>
</tr>
<tr>
<td>SAPS II†</td>
<td>1.06 (1.03 - 1.08)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Respiratory Compliance‡</td>
<td>1.06 (1.01 - 1.10)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* per increase of 0.05  † per 1 point increase  ‡ per decrease of 1 ml/cm H$_2$O
Early Elevation of Dead Space Fraction in ARDS

Nuckton T et al, NEJM, 2002
Dead Space and Mortality in Early ARDS
An Elevated Dead Space Fraction Is Associated with Mortality in ARDS

NEJM 346:1281-6, 2002
Pulmonary Dead Space in ARDS in 53 Patients Ventilated for at least 6 Days

Kallet et al, 2004
Predictive Value of Dead Space in Follow Up Study

- 42 patients with ARDS measured Vd/Vt by volume capnography (NICO) and all patients ventilated with 6 ml/kg ideal body weight tidal volume

- Baseline pulmonary dead space was predictive of death (0.61 ± .09 vs 0.53 ± .10, p < .01)

Cepkova et al, Chest, 2007
Studies from other Investigators

• Gattinoni et al, NEJM 2006 – Elevated dead space has predictive value for mortality in ARDS.

• Ong et al, Crit Care Med 2010 – Elevated dead space + Ang-2/Ang-1 ratio predictive of mortality in 56 patients with ALI.

• Lucagelo et al – Chest 2010 – Elevated dead space a good predictor of mortality.
Mechanisms that Account for the Increase in the Dead Space Fraction in Early ARDS

- Thrombotic / inflammatory injury to the lung microcirculation
- Obstruction of blood flow in the extra-alveolar lung circulation
- Areas of high ratio of ventilation to perfusion
Macrovascular Obstruction in ARDS: Detection with Balloon Occlusion Pulmonary Angiography (BOPA)

- BOPA + in 19 of 40 between 1-17 days after ARDS onset
- Filling defects a/w 1) ARDS severity 2) presence of DIC 3) PA HTN 4) fatal outcome

Green et al ARRD 1982
Microvascular Obstruction and Remodeling in ARDS

Normal human lung capillaries | Lung capillaries p 14 d ARDS

Morphometric analysis -> Thrombosis, medial thickening, decreased vascular density of pre- and intra-acinar vessels

Zapol et al Chest, 1977; Snow et al ARRD 1982
Estimating Dead-Space Fraction

• Rationale
  – No validated estimate of $V_D/V_T$ exists

• Four estimates of $V_D/V_T$ evaluated
  – 3 estimate energy expenditure to predict $VCO_2$
    • Unadjusted Harris-Benedict equation
    • Harris-Benedict equation with hypermetabolic factors (Siddiki et al)
    • Penn State equation for critically ill (Frankenfield et al)
  – 1 estimate modeled $V_D/V_T$ directly

Estimating Dead-Space Fraction

HB predicted measured $V_D/V_T$ to within $\pm 0.10$ in 70% of patients, and within $\pm 0.20$ in 95% patients.

HB less accurate when $\text{PaCO}_2 < 30$

Estimating Dead-Space Fraction

- Harris-Benedict best mirrors measured $V_D/V_T$ association with mortality

- Mortality within ± 6.7% of measured $V_D/V_T$ for all quintiles

- Improved predictive validity for mortality when added to Berlin definition
  - ROC 0.714 vs 0.543, $p < .01$

- $OR_{death}$ per 0.05 increase in $V_D/V_T$, multivariable analysis:
  - Measured: 1.36 (1.10-1.68)
  - Harris-Benedict: 1.55 (1.21-1.98)

Conclusions: Estimating Dead-Space Fraction

- $V_D/V_T$ should be measured in future RCTs to facilitate secondary analyses to shape research & practice
- Harris-Benedict estimate best predicts the measured $V_D/V_T$ and association with mortality on group level
  • Enhanced predictive validity over Berlin definition alone
  • But not adequate for individual care: accurate to within $\pm 0.10$ in 70% of patients

Table 2. Comparison of Dead-Space Fraction and Mean Expired Carbon Dioxide Partial Pressure Made by Metabolic Monitor and Volumetric Capnography

<table>
<thead>
<tr>
<th></th>
<th>Delta-trac Uncorrected</th>
<th>Delta-trac Corrected</th>
<th>NICO Monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{eCO_2}$ (mm Hg)</td>
<td>15.7 ± 4.7</td>
<td>18.5 ± 5.7</td>
<td>17.5 ± 5.5</td>
</tr>
<tr>
<td>$V_D/V_T$</td>
<td>0.64 ± 0.11</td>
<td>0.58 ± 0.14</td>
<td>0.60 ± 0.12</td>
</tr>
</tbody>
</table>

$P_{eCO_2} =$ mean expired carbon dioxide partial pressure

$V_D/V_T =$ physiologic dead-space-to-tidal-volume ratio

Kallet R et al
Conclusions

• Elevated dead space fraction predicts mortality in ARDS, a finding with pathogenetic significance.

• Thrombotic and inflammatory injury to the lung microcirculation is probably a major early mechanism of lung injury in ARDS.

• Measurement of pulmonary dead space should be done in clinical research and trials in ARDS.