The Importance of Spontaneous Breathing during Mechanical Ventilation

Tom Malinowski, RRT, FAARC
Director, Respiratory Services, Community Asthma Awareness Program
Mary Washington Healthcare
Fredericksburg, VA
Objectives

- Review the theoretical importance of spontaneous breathing on diaphragmatic function.
- Review the laboratory and human subject evidence of mechanical ventilation on diaphragmatic activity.
- Review the impact of daily SAT/SBT trials.
Author Disclosure/Conflict of Interest Statement

- I have no financial interests in the lucrative and profitable diaphragm-function industry nor do I work for the multiple for-profit or not-for-profit spontaneous breathing coalitions that exist on Capitol Hill...
Respiratory Power

- Diaphragm - extremely active muscle, (30-40% activity, 24 hrs./day)
- Capacity to increase Ve 15 – 30-fold
- Composed of slow and fast twitch fibers
- Developmental and Disease specific modifications
Characteristics of Diaphragm Muscle Fibers
Form and Function

Pro Cycling *tifosi*

Pro Cyclist
How Much Work are We Capable of?

Elite athletes - 185 - 200 LPM of Minute Ventilation
Premise – Pts. with Acute Respiratory Failure should be rested…

- Resting reduces pt work-of-breathing
- Resting reduces VO$_2$ by respiratory muscles
  - As much as 15-20% of total VO2 under extremis
- Resting prepares for weaning
- What possibly could be *wrong* with not breathing?
Ventilator Induced Diaphragmatic Dysfunction (VIDD)

- Adverse effect of mechanical ventilation on ventilatory muscles
- 40-50% reduction in pressure generating within 3-6 days of controlled mech vent.
  - Reduction in endurance
  - Reduction in force
- Not related to a change in nerve impulse
Ventilator Induced Diaphragmatic Dysfunction (VIDD)

- Characterized by a reduction in the force-generating capacity of the diaphragm.
  - Trans-diaphragmatic pressure generation is reduced
  - Reduction in endurance
- Usually time-dependent
- Majority of evidence from animal or in vitro studies
Probable Causes of VIDD

- Muscle atrophy – absence of use
  - Decreased protein synthesis
  - Protein breakdown
- Fiber Remodeling
  - Muscle specific proteins
  - Oxidative stress – protein oxidation
- Structural injury
  - Disruption of myofibrils
  - Abnormal mitochondria
- Metabolic enzymes – decreasing efficiency
- Gene expression – ultimate cause?
Muscle Atrophy

- Decreased protein synthesis
- Increased proteolysis
- 1 – 11 days
  - 40-50% reduction in diaphragmatic force
  - Baboon, piglet models
- Not related to lung volume, abdominal compliance, nerve impulse transmission

CCM 1997;25: 1187-1190
What is the Consequence of not Using the Diaphragm?

- The diaphragm fires 30-40% of the day
- More active than other skeletal muscle
- Normal exposure to a negative pressure
  - Stretch-like stimulus
- CMV = “Disuse”?
  - Unload the diaphragm
  - Cyclical inflation with PEEP, positive pressure
Impact of Assisted Ventilation vs. Controlled Ventilation

Sassoon, AJRCCM 2004; 170: 626-32
Conditions Increasing VIDD Risk

- Prolonged neuromuscular blockade
- Critical Illness Polyneuropathy
  - Sepsis
  - Hyperglycemia
  - Corticosteroids
  - Neuromuscular blockers
Hypothesis for weaning failure with controlled mechanical ventilation

CMV

Further “Rest”
Failure

Atrophy, wasting, disuse

Weaning failure

Fatigue, Injury on re-initiation of efforts
Comparison of biopsy specimens

- 8 control pts
  - 2-3 hrs. of mechanical ventilation
- 14 brain-dead organ donors (case pts.)
  - 18 – 69 hrs. of CMV
<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>BMI</th>
<th>Reason for Surgery or Cause of Brain Death</th>
<th>Relevant Medical History</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control subjects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>79</td>
<td>M</td>
<td>31</td>
<td>Stage 1A adenocarcinoma of the lung</td>
<td>Prostate carcinoma, nonsmoker, farmer</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>M</td>
<td>36</td>
<td>Stage 1A adenocarcinoma of the lung</td>
<td>Peripheral arterial disease, rheumatoid arthritis, hypertension, coronary artery disease, smoked 90 pack/yr</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>F</td>
<td>23</td>
<td>Stage 1A benign fatty tumor</td>
<td>Hypercholesterolemia, osteoarthritis, smoked 10 pack/yr</td>
</tr>
<tr>
<td>4</td>
<td>76</td>
<td>M</td>
<td>27</td>
<td>Stage 1A adenocarcinoma of the lung</td>
<td>Coronary artery disease with history of myocardial infarction, muscular degeneration, prostate carcinoma (radiation therapy, 1999), coronary-artery bypass graft (1988), pipe smoker (quit 30 yr ago)</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>F</td>
<td>30</td>
<td>Stage 1 carcinoid tumor</td>
<td>Hypercholesterolemia, primary hyperparathyroidism, kidney stones, smoked 40 pack/yr</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>F</td>
<td>27</td>
<td>Ganglioneuroma</td>
<td>Gallstones, nonsmoker</td>
</tr>
<tr>
<td>7</td>
<td>54</td>
<td>F</td>
<td>23</td>
<td>Ganglioneuroma</td>
<td>Glaucoma, seasonal allergies, nonsmoker</td>
</tr>
<tr>
<td>8</td>
<td>41</td>
<td>F</td>
<td>26</td>
<td>Hamartoma</td>
<td>Herniated lumbar disks, dysfunctional uterine bleeding, smoked 24 pack/yr (quit 2 yr ago)</td>
</tr>
<tr>
<td><strong>Case subjects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>18</td>
<td>F</td>
<td>24</td>
<td>Motor vehicle accident</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>F</td>
<td>29</td>
<td>Drug overdose</td>
<td>Drug abuse</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>M</td>
<td>25</td>
<td>Gunshot wound to head</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>M</td>
<td>24</td>
<td>Respiratory arrest secondary to seizure</td>
<td>Seizure disorder with implanted pacemaker</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>M</td>
<td>24</td>
<td>Motor vehicle accident</td>
<td>Hypertension, peptic ulcer disease, depression, hypogonadism, smoker</td>
</tr>
<tr>
<td>6</td>
<td>33</td>
<td>F</td>
<td>44</td>
<td>Drug overdose</td>
<td>Drug and ethyl alcohol abuse, metronidazole and cotrimoxazole for vaginitis</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>F</td>
<td>21</td>
<td>Motor vehicle accident</td>
<td>Pregnant</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>M</td>
<td>21</td>
<td>Stroke</td>
<td>Hypertension, ethyl alcohol abuse, smoked 30 pack/yr</td>
</tr>
<tr>
<td>9</td>
<td>23</td>
<td>M</td>
<td>20</td>
<td>Motor vehicle accident</td>
<td>Hypertension, ethyl alcohol abuse, marijuana abuse</td>
</tr>
<tr>
<td>10</td>
<td>53</td>
<td>F</td>
<td>45</td>
<td>Stroke</td>
<td>Hypertension, type 2 diabetes mellitus, gastroesophageal reflux disease, atrial fibrillation (new onset)</td>
</tr>
<tr>
<td>11</td>
<td>45</td>
<td>M</td>
<td>32</td>
<td>Stroke</td>
<td>Hypertension, ethyl alcohol abuse, drug abuse</td>
</tr>
<tr>
<td>12</td>
<td>26</td>
<td>M</td>
<td>28</td>
<td>Cardiac arrest</td>
<td>Seizure disorder</td>
</tr>
<tr>
<td>13</td>
<td>56</td>
<td>F</td>
<td>26</td>
<td>Stroke</td>
<td>Smoked 80 pack/yr</td>
</tr>
<tr>
<td>14</td>
<td>58</td>
<td>F</td>
<td>36</td>
<td>Stroke</td>
<td>Hypertension, chronic obstructive pulmonary disease, hypothyroidism, schizoaffective disorder, bipolar disorder, smoked 25 pack/yr, obesity, oral corticosteroid prescription</td>
</tr>
</tbody>
</table>

* All control subjects had normal values for spirometry. BMI denotes body mass index (defined as the weight in kilograms divided by the square of the height in meters).
<table>
<thead>
<tr>
<th>Measurement</th>
<th>Control Subjects (N=8)</th>
<th>Case Subjects (N=14)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ventilator settings and related measurements</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tidal volume (ml/kg of body weight)</td>
<td>7.5±1.3</td>
<td>8.0±2.0</td>
<td>0.47</td>
</tr>
<tr>
<td>Ventilation frequency (breaths/min)</td>
<td>11±1.7</td>
<td>14±3.0</td>
<td>0.02</td>
</tr>
<tr>
<td>PEEP (cm H₂O)</td>
<td>0.0±0.0</td>
<td>6.0±1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FiO₂ (%)</td>
<td>—</td>
<td>52±0.11</td>
<td>—</td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>99±2.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PaO₂ (mm H₂O)</td>
<td>—</td>
<td>147±88</td>
<td>—</td>
</tr>
<tr>
<td>PETCO₂ (mm Hg)</td>
<td>31±3.8</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>—</td>
<td>34±6.0</td>
<td>—</td>
</tr>
<tr>
<td>Arterial pH (units)</td>
<td>—</td>
<td>7.39±0.05</td>
<td>—</td>
</tr>
<tr>
<td>PaO₂/FiO₂†</td>
<td>—</td>
<td>412±167</td>
<td>—</td>
</tr>
<tr>
<td><strong>Vital signs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>115±10</td>
<td>125±20</td>
<td>0.20</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>62±6.0</td>
<td>70±10</td>
<td>0.08</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>72±9.0</td>
<td>105±18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>35.7±0.3</td>
<td>36.4±1.1</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* Plus-minus values are means ±SD. FiO₂ denotes fractional concentration of inspired oxygen, PaCO₂ arterial carbon dioxide pressure, PaO₂ arterial oxygen pressure, PEEP positive end-expiratory pressure, PETCO₂ end-tidal carbon dioxide pressure, and SaO₂ arterial oxygen saturation.
†† These measurements were made at an FiO₂ of 1.0.
18-69 hrs. of Diaphragmatic Inactivity and CMV

- Atrophy of both slow and fast-twitch fibers
- Increase in oxidative stress markers
- Increased proteolysis
Comparative Cross Section

NEJM 2008; 358:1327 -35
Possible pathways of diaphragm atrophy and weakness

AJRCCM 2007;175: 1233-1240
Several of the mechanistic pathways implicated in the development of VIDD are illustrated. Protein synthesis pathways are downregulated (indicated by dashed lines). In addition, ROS generated from several possible sources can activate downstream proteolytic pathways involved in myofiber injury and atrophy, including the calpain and caspase systems; these have the potential to be mutually reinforcing and to drive further ROS production. The role of lysosomally-mediated proteolysis, and particularly autophagy, remains to be explored. IGF-1, insulin-like growth factor-1; MV, mechanical ventilation; PI3K, phosphoinositide-3 kinase; ROS, reactive oxygen species.
Diaphragmatic Pacing

- Avoidance of muscle atrophy
- Improvement in tidal volume
- Augmentation of ventilatory support
- Site familiarity
Spontaneous Breathing…It’s just the right thing to do…

- Induces improvement in distribution of ventilation
- Improvement in V/Q
- Avoidance of alveolar collapse
- Preservation of muscular function, integrity
Presence of spontaneous breathing resulted in a significant decrease in the lung volume with HUs ranging between −100 and 100, indicating non-aerated lung areas, while the lung volume with HUs ranging between −900 and −500 indicated normal aerated lung areas were increased. These observations indicate alveolar recruitment with spontaneous breathing.
Sedation Awakening and SBT

- Daily SBT demonstrated statistical and clinically significant ↓ in duration of CMV*.
- Daily interruption of sedation ↓ CMV duration and ↓ ICU LOS Δ.
- Combining both sedation awakening and SBT produced ↓ in duration of CMV, ICU stay and ↓ mortality±.

*Ely W, et. al, NEJM 1996; 335:1864-69
ΔKress J, et. al, NEJM 2000; 342: 1471-1477
±Girard T, et. al, Lancet 2008; 371:126-34
RCT in 4 hospitals

- 336 patients
- Control – Sedation as usual, daily SBT
- Intervention – Daily SAT and SBT

Lancet 2008; 371: 126-34
"Wake Up and Breathe" Protocol
Spontaneous Awakening Trials (SATs) + Spontaneous Breathing Trials (SBTs)

**SAT Safety Screen**
- No active seizures
- No alcohol withdrawal
- No agitation
- No paralytics
- No myocardial ischemia
- Normal intracranial pressure

**SAT Failure**
- Anxiety, agitation, or pain
- Respiratory rate > 35/min
- SpO2 < 88%
- Respiratory distress
- Acute cardiac arrhythmia

**SBT Safety Screen**
- No agitation
- Oxygen saturation ≥ 88%
- FiO2 ≤ 50%
- PEEP ≤ 7.5 cm H2O
- No myocardial ischemia
- No vasopressor use
- Inspiratory efforts

**SBT Failure**
- Respiratory rate > 35/min
- Respiratory rate < 8/min
- SpO2 < 88%
- Respiratory distress
- Mental status change
- Acute cardiac arrhythmia

*Adapted from Girard TD et al. Lancet 2008;371:126-34*
<table>
<thead>
<tr>
<th></th>
<th>Intervention group (n=167)</th>
<th>Control group (n=168)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ventilator-free days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>14.7 (0.9)</td>
<td>11.6 (0.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Median</td>
<td>20.0 (0 to 26.0)</td>
<td>8.1 (0 to 24.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Time to discharge (days)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From intensive care</td>
<td>9.1 (5.1 to 17.8)</td>
<td>12.9 (6.0 to 24.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>From hospital</td>
<td>14.9 (8.9 to 26.8)</td>
<td>19.2 (10.3 to NA)†</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>28-day mortality</strong></td>
<td>47 (28%)</td>
<td>58 (35%)</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>1-year mortality</strong></td>
<td>74 (44%)</td>
<td>97 (58%)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Duration of brain dysfunction (days)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coma</td>
<td>2 (0 to 4)</td>
<td>3 (1 to 7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Delirium</td>
<td>2 (0 to 5)</td>
<td>2 (0 to 6)</td>
<td>0.50</td>
</tr>
<tr>
<td>RASS at first successful SBT</td>
<td>-1 (-3 to 0)</td>
<td>-2.5 (-4 to 0)</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any self-extubation</td>
<td>16 (10%)</td>
<td>6 (4%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Self-extubation requiring reintubation†</td>
<td>5 (3%)</td>
<td>3 (2%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Reintubation†</td>
<td>23 (14%)</td>
<td>21 (13%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>21 (13%)</td>
<td>34 (20%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Data are mean (SD), n (%), or median (IQR). RASS=Richmond agitation-sedation scale. SAT=spontaneous awakening trial. SBT=spontaneous breathing trial. *Ventilator-free days from study day 1 to 28. †Greater than 25% of patients in the SBT group remained in the hospital at study day 28. ‡Reintubation within 48 hours of extubation.

Table 3: Main outcomes
Lancet 2008; 371: 126-34
Reasons for “Missed Opportunities” with SAT or SBT Attempts

- Physician Orders
- Staffing
- Education
- Initiative
Mechanical Ventilation without Initiation of Inspiratory Efforts…

- Leads to disuse, atrophy
  - Reduction in tidal volume, inspiratory capacity
- Leads to fatigue
- Leads to “resting” without work
- Leads to injury with a return to normal work levels and subsequent weaning failure
Take Home

- Patient initiation of breathing is a good thing
- Multiple factors influence weaning
  - Pharmacologic, Pathophysiology
  - Ventilator management
- Animal, human data imply diaphragmatic wasting occurs in a very short period of time (< 24 hrs.) with controlled MV.
- No evidence of PS, A/C, IMV superiority
- There is strong evidence that daily SAT/SBT’s are the right thing to do…
References

- Vassilakopoulos, Petrof B; Ventilator-induced Diaphragmatic Dysfunction AJRCCM 2004; 169: 336-41
- VENITLA Group; Evolution of Mechanical Ventilation in Response to Clinical Research AJRCCM 2008; 177: 170-77
- Levine et. al.: Rapid Disuse Atrophy of Diaphragm Fibers in Mechanically Ventilated Humans. NEJM 2008; 358: 1327-35
- Girard et. al.: Efficacy and Safety of a Paired Sedation and Ventilator Weaning Protocol for Mechanically Ventilated Patients in Intensive Care (Awakening and Breathing Controlled Trial): a Randomized Controlled Trial. Lancet 2008; 371: 126-34