Pulmonary Physiology in Spinal Cord Injury: New Insights and Possible Therapeutic Interventions

Gregory J. Schilero, M.D., F.C.C.P.
Pulmonary/Critical Care/Sleep Medicine
Co-Director, Pulmonary Research Section, Center of Excellence for the Medical Consequences of Spinal Cord Injury
The James J. Peters VA Medical Center, Bronx, N.Y.
Assistant Professor of Medicine, The Mount Sinai School of Medicine, New York, N.Y.
I have no financial interests or relationships to disclose.
At the conclusion of this activity, the participant will be able to:

- **A.** Understand how respiratory muscle paralysis affects inspiratory and expiratory muscle function in persons with SCI

- **B.** Appreciate the potential role of autonomic imbalance and airway inflammation in the pathogenesis of airflow obstruction and airway hyperreactivity in persons with tetraplegia

- **C.** Identify potential pharmacologic interventions to reduce pulmonary complications in persons with SCI
Pulmonary Physiology in SCI

- Paralysis of Respiratory Muscles
  - Restrictive pulmonary dysfunction
  - Cough Effectiveness

- Airway Dynamics
  - Bronchodilator responsiveness
  - Nonspecific airway hyperreactivity (AHR)
  - Baseline airway caliber
  - Autonomic Nervous System
  - Airway Inflammation

Respiratory Symptoms

Augmenting Bronchodilation and Respiratory Muscle Strength
- Ongoing Research
INNERVATION OF PRINCIPAL MUSCLES OF RESPIRATION

- Innervation of the Diaphragm
  - C3 to C5

- Innervation of the Intercostal and Abdominal Muscles
  - T1-T12
Inspiratory muscle weakness

- Diaphragmatic innervation retained
  - Suboptimal resting muscle length due to chest cage distortion
- Denervation of intercostal muscles with cervical injury
- Decreased TLC, static maximal inspiratory pressure (MIP)

Expiratory muscle weakness

- Denervation of intercostal muscles and abdominal musculature with higher levels of injury
- Decreased FVC, ERV, static maximal expiratory pressure (MEP)
- Increased RV
LUNG VOLUME RESTRICTION

Restriction
Slight ↓ TLC
↓↓ FVC
↓↓ ERV
↑ RV
Fitted Values for FVC Percent Predicted by Vertebral Level for Complete Motor Lesions

Ineffective cough

Retained secretions
  • Atelectasis -> pneumonia

↑’d Risk of pulmonary complications
  • major cause of morbidity and mortality

RESIDUAL EXPIRATORY MUSCLE FUNCTION IN TETRAPLEGIA

Clavicular Portion of Pectoralis Major and Cranial Portion of the Serratus Anterior

Latissimus dorsi

Teres Major

Bronchodilator Responsiveness

Airway Caliber

Nonspecific Airway Hyperreactivity (AHR)
41% of 34 subjects had a significant bronchodilator response to metaproterenol sulfate (> 12% ↑ FEV₁ and ↑ 200ml)

48% of 25 subjects had a significant bronchodilator response to ipratropium bromide


Interruption of sympathetic innervation

Heightened vagal airway tone

Role of Airway Inflammation

Bronchodilator responsiveness
  - ipratropium bromide > beta-2 adrenergic agonists
Bronchodilation (norepinephrine)

Bronchoconstriction (acetylcholine)

Reduced baseline airway caliber due to overriding cholinergic airway tone
ANS CONTROL OF AIRWAYS
NON-SPECIFIC AIRWAY HYPERREACTIVITY (AHR) IN TETRAPLEGIA

- Majority of subjects manifest non-specific AHR following pretreatment with histamine, methacholine, and UNDW
- Response similar to that found in mild asthma

25 of 32 tetraplegic subjects exhibited hyperresponsive to histamine

Responders had lower FEV₁% predicted, FEF 25-75%, and FEF 25-75/FVC

Findings suggested that subjects with tetraplegia had reduced baseline airway caliber

15 subjects with tetraplegia, 15 with paraplegia, 15 controls

Measured specific airway conductance (sGaw) before and after ipratropium bromide
**SPECIFIC AIRWAY CONDUCTANCE**
(cm $H_2O^{-1}s^{-1}$)

<table>
<thead>
<tr>
<th></th>
<th>sGaw</th>
<th>IB-sGaw</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetra (15)</td>
<td>0.16±0.05†</td>
<td>0.31±0.11‡</td>
<td>93</td>
</tr>
<tr>
<td>Para (15)</td>
<td>0.26±0.05</td>
<td>0.31±0.03</td>
<td>19</td>
</tr>
<tr>
<td>Cont (15)</td>
<td>0.27±0.05</td>
<td>Not Done</td>
<td>Not Done</td>
</tr>
</tbody>
</table>

† significantly lower when compared to paraplegia and control group
‡ significant change from baseline following ipratropium bromide

REDUCED BASELINE AIRWAY CALIBER
**Figure 1.** Representation of the raw signal to obtain exhaled levels of NO. Green line represents the exhaled breathe flow rate; Red line represents NO levels. Exhaled NO levels are calculated over a 3 second period during a stable flow rate of 12 liters per second.
Radulovic M, Schilero GJ, Wecht JM, LaFountaine M, Rosado-Rivera D, Bauman WA. Exhaled nitric oxide levels are elevated in persons with tetraplegia and comparable to that in mild asthmatics. *Lung* 2010; 188(3): 259-262.

**Figure 2.** Representation of exhaled nitric oxide levels in parts per billion (ppb) by group. Values are reported as Group mean (±SD).
SUMMARY OF PHYSIOLOGIC FINDINGS

- **Respiratory Muscle Weakness**
  - Inspiratory and expiratory muscles
  - Decreased cough effectiveness
  - Increased risk of pulmonary complications
    - Atelectasis/pneumonia

- **Reduction in baseline airway caliber in Tetraplegia**
  - Baseline bronchoconstriction
    - Heightened cholinergic airway tone
    - Role of Airway Inflammation ?

- ** Significant bronchodilator responsiveness in Tetraplegia**
  - Restoration of normal airway caliber after inhalation of short-acting bronchodilators
  - Ipratropium bromide > beta-2 adrenergic agonist (albuterol)

- **Nonspecific airway hyperreactivity**
  - Autonomic Imbalance ?
  - Role of Airway Inflammation ?
Survey of 180 with SCI

68% of all subjects reported one or more symptom

BREATHLESSNESS ASSOCIATED WITH IRRITANTS

- cold air
- hot air
- smoke
- perfume
- hairspray
- other

- High Tetra
- Low Tetra
- High Para
- Low Para

Percent

* indicates significant difference.
WAYS TO IMPROVE EXPIRATORY MUSCLE STRENGTH

- Expiratory resistance devices
  - variable results in small trials

- Training of the clavicular portion of the pectoralis muscle

- Anabolic agents (beta-2 agonists)
Numerous animal studies have shown that beta-2 agonists improve muscle mass and strength. Beta-2 agonist amplified total work output during functional electrical stimulation. Induced a significant increase in muscle size and strength of the forearm in 10 subjects with tetraplegia.


Randomized, prospective, double-blind, placebo-controlled with crossover

**Phases**
- baseline
- treatment 4 weeks
- washout 4 weeks
- treatment 4 weeks
- follow-up 4 weeks

11 subjects with tetraplegia
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Placebo</th>
<th>Salmeterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC (L)</td>
<td>5.20±0.47</td>
<td>5.11±0.48</td>
<td>5.32±0.32</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>3.11±0.38</td>
<td>3.22±0.41</td>
<td>3.36±0.41*†</td>
</tr>
<tr>
<td>FEV$_1$ (L)</td>
<td>2.40±0.51</td>
<td>2.52±0.49</td>
<td>2.74±0.52*†</td>
</tr>
<tr>
<td>ERV (L)</td>
<td>0.51±0.20</td>
<td>0.55±0.17</td>
<td>0.60±0.20‡</td>
</tr>
<tr>
<td>FRC (L)</td>
<td>2.58±0.33</td>
<td>2.47±0.34</td>
<td>2.60±0.27</td>
</tr>
<tr>
<td>RV (L)</td>
<td>2.11±0.45</td>
<td>1.89±0.41</td>
<td>1.98±0.44</td>
</tr>
<tr>
<td>MIP (cmH$_2$O)</td>
<td>72.5±18.6</td>
<td>73.9±21.5</td>
<td>81.6±20.8*†</td>
</tr>
<tr>
<td>MEP (cmH$_2$O)</td>
<td>40.9±16.6</td>
<td>45.9±19.2</td>
<td>51.3±20.0*†</td>
</tr>
</tbody>
</table>

*p<0.001 vs. baseline; †p<0.05 vs. placebo; ‡p<0.05 vs. baseline; L=liters
MAXIMUM STATIC PRESSURES

Figure 1

Percent Change from Baseline

BL | Phase 2 | Phase 4

- MIP placebo first
- MIP salmeterol first
- MEP placebo first
- MEP salmeterol first
SALMETEROL STUDY

- Induced long-term bronchodilation
- Changes in MEP and MIP may have been associated with bronchodilation
- Sustained increase in MEP and MIP among those who received salmeterol first suggests a positive effect on respiratory muscles

Maintenance therapy with inhaled anticholinergic agents in persons with tetraplegia will be associated with:

- Bronchodilation and normalization of airway caliber

And will possibly be associated with:

- Attainment of greater lung volumes during cough for expulsion of secretions
- Decrease in airway hyperreactivity
- Reduction in respiratory symptoms and improved quality of life
- Reduction in pulmonary complications
Maintenance therapy with either an oral or long-acting inhaled beta-2 adrenergic agonist in persons with SCI will be associated with:

- Significant bronchodilation
- Decrease in airway hyperreactivity

And will possibly be associated with:

- Improvement in inspiratory and expiratory muscle strength
- Attainment of greater force generation during cough for expulsion of secretions
- Reduction in respiratory symptoms and improved quality of life
- Reduction in pulmonary complications
Ongoing Research

- Effects of an oral beta-2 agonist (albuterol sulfate), with or without an inspiratory/expiratory resistance training device, upon measures of pulmonary function, work of breathing, respiratory muscle strength, respiratory symptoms, and cough effectiveness.

- Effects of a long-acting anticholinergic agent (tiotropium bromide) upon pulmonary function, respiratory symptoms, quality of life, and disease-specific mortality.

- Assessment of cellular inflammation in airways
  - Sputum analysis
  - Exhaled biomarkers of inflammation
    - Isoprostane-8
  - Effects of inhaled corticosteroids
Beta-2 Agonist to Increase Respiratory Muscle Strength

- Study groups
  - 20 Tetraplegia
  - 16 High Paraplegia

- Double blind, randomized, placebo-controlled

- 12 weeks of placebo vs. oral beta-2 agonist

- Pre- and post- measurements of PFT's, MIP/MEP, transpulmonary pressures, cough strength, diaphragmatic thickness, work of breathing

- Option to continue in study additional 6 weeks using inspiratory/expiratory resistance device
CENTER OF EXCELLENCE FOR MEDICAL CONSEQUENCES OF SPINAL CORD INJURY

- Dr. William Bauman
- Dr. Ann M. Spungen
- Dr. Jill M. Wecht
- Dr. Christopher Cardozo
- Dr. Gregory Schilero
- Dr. Miroslav Radulovic
- Dr. Mark Korsten
- Dr. Marvin Lesser

- Dr. Michael LaFountaine
- Dr. Dwindally Rosado
- Dr. John Handrakis
- Christina Yen
- Christopher P. Renzi
- Christopher Cirnigliaro
- Marley Jensen
Obtaining CME Credit

- If you would like to receive CME credit for this activity, please visit:

- This information can also be found in the Summit 2011 Program on page 8.