Neural control of airways in COPD

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February 2019
Nerve innervation of the lung is extensive

Whole mouse lung stained with fluorescent pan-neurofilament antibody
Lung denervation alters lung physiology

- Vagotomy decreases airflow resistance
- Stimulation of vagus nerve causes bronchoconstriction
- Vagotomy decreases airflow resistance
- Vagotomy abolishes airway basal tone
- Vagotomy abolishes reflex mucus hypersecretion
- Vagotomy reduces airway inflammatory response to particulate exposure
- Vagotomy abolishes airway hyperactivity (viral infection)
- Bilateral vagotomy relieves intractable asthma
- Unilateral vagotomy improves symptoms of breathlessness in emphysematous patients
- Hypoxia induced airway narrowing absent in lung transplant patients
- Pharmacologic block of vagus nerve relieves symptoms of dyspnea

- ↓ resistance to airflow
- ↓ mucus hypersecretion
- ↓ inflammation
- ↓ hyperresponsive airways
- ↓ perception of dyspnea/cough
Disruption of vagus nerve signaling is a logical therapeutic target in COPD management

Pulmonary vagal nerves (vagal afferent and parasympathetic efferent) are mediators of COPD pathophysiology\(^1\)

- Airflow limitation and gas trapping\(^2\)
  - Increased basal parasympathetic smooth muscle tone
- Mucus hypersecretion\(^3,4,5\)
  - Innervate and stimulate submucosal gland hypersecretion
- **COPD Exacerbations (AECOPD)\(^6,7,8,9,10\)**
  - Neuro-hyperresponsiveness contributes to airway hyperresponsiveness and increased symptom burden during exacerbation

2. Colebatch et al J Appl Physiol 1963
Vagal nerve meditates tonic control of airway smooth muscle

Electrical stimulation of the vagus nerve produces immediate increases in airway resistance.

Bilateral cervical vagotomy produced reduced inspiratory resistance to airflow.

Vagal nerve mediates tonic control of smooth muscle in the lungs

*indicated p < 0.05 vs intact vagal control

**Table 1. Effect of vagotomy on lung mechanics**

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of Animals</th>
<th>Lung compliance, ml/cm H₂O kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>13</td>
<td>3.53±2.05*</td>
</tr>
<tr>
<td>V</td>
<td>8</td>
<td>2.16±0.77*</td>
</tr>
<tr>
<td>Inf</td>
<td>13</td>
<td>3.71±2.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of Animals</th>
<th>Tidal volume, ml/m² BSA, BTPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>13</td>
<td>286±58</td>
</tr>
<tr>
<td>V</td>
<td>13</td>
<td>425±91</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of Animals</th>
<th>No. of breaths/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>13</td>
<td>43.8±13.8</td>
</tr>
<tr>
<td>V</td>
<td>13</td>
<td>24.6±7.5*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of Animals</th>
<th>Ventilation, liters/min m² BSA, BTPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>13</td>
<td>12.2±3.43</td>
</tr>
<tr>
<td>V</td>
<td>13</td>
<td>10.0±2.87†</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of Animals</th>
<th>Insp. resist. to airflow, cm H₂O/liter sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>8</td>
<td>1.23±0.22</td>
</tr>
<tr>
<td>V</td>
<td>8</td>
<td>0.96±0.24*</td>
</tr>
</tbody>
</table>

Colebatch et al J Appl Physiol 1963
Changing basal cholinergic tone impacts AECOPD

Pharmacologic bronchodilation reduce AECOPD (UPLIFT, POET, MISTRAL)

Proposed mechanism of action
- improvement in hyperinflation
- resets threshold of at which an exacerbation is triggered

Increases in bronchodilation and lung hyperinflation
- associated with recovery from AECOPD
- Hyperinflation improvement better indicator of exacerbation recovery than FEV$\textsubscript{1}$

1. Vogelmeier et al NEJM 2011
3. Geffen et al Int J COPD 2018
5. Miravitlles et al Eur Respir Rev 2010
Vagal nerve modulates mucus hypersecretion

Submucosal glands densely innervated by parasympathetic system

Stimulation of parasympathetic efferents increase secretion rates to ~2x the basal rate.

Sensory axons (C fibers and stretch receptors) stimulate mucus secretion via central reflexes.

Glands from chronic bronchitis, COPD and cystic fibrosis patients exaggerated response to nerve input.

1. Cuthbert et al Physiological Reports 2015
5. Davis et al J Appl Physiol 1982
6. Sturgess et al Exper and Mol Path 1972
Lung Nerve structure/function: Reflex bronchoconstriction

- Peripheral nerve neurons
  - Soma or cell body
    - Sensory neuron: ganglia near CNS
    - Motor neuron: within CNS
  - Axon
    - Projects from soma to target

- Sensory neuron, vagal afferent
- Motor neuron, parasympathetic efferent
- Parasympathetic Ganglia
- Sensory Afferent Action potential (AP)
- Motor Efferent Action potential (AP)
- Jugular and Nodose ganglia
- Lung Nerve structure/function: Reflex bronchoconstriction
  - 1) Acute stimuli
  - 2) Sensory AP
  - 3) Motor AP
  - 4) Activation of Pulmonary ganglion
  - 5) ACh release: Bronchoconstriction Mucus Hypersecretion
Reflex bronchoconstriction mediated by Vagus nerve

Vagotomy abolishes reflex bronchoconstriction
- Evolutionarily conserved reflex across multiple species

Lung Nerve structure/function: Airway hyperresponsiveness

- **Peripheral nerve neurons**
  - **Soma or cell body**
    - Sensory neuron: ganglia near CNS
    - Motor neuron: within CNS
  - **Axon**
    - Projects from soma to target

- Sensory neuron, vagal afferent
- Motor neuron, parasympathetic efferent
- Parasympathetic Ganglia
- Sensory Afferent Action potential (AP)
- Motor Efferent Action potential (AP)

1) Acute stimuli
2) Exaggerated Sensory AP
3) Exaggerated Motor AP
4) Increased activation of Pulmonary ganglion
5) Hyper ACh release: Bronchoconstriction Mucus Hypersecretion
Vagal nerve essential to bronchial hyperresponsiveness

- Vagotony reverses hyperresponsiveness associated with chronic/acute inflammation\(^1\)

- Vagotomy reverses hyperresponsiveness associated with viral infection\(^2\)

- Hyperactive sensory fibers in inflammatory environment contribute to increased symptoms\(^3,4\)

4. Drake et al. Sci Trans Med 2018
Airway hyper-responsiveness and Exacerbations

“Airway hyper-responsiveness can exist without diagnosis of asthma and has been shown to be an independent predictor of COPD and respiratory mortality in population studies....” -- GOLD 2018

Airway hyper-responsiveness in COPD patients

- Associated with long-term mortality in COPD (p < 0.05)1
- Correlated to worsening symptom score (r = 0.87)2
- Correlated to prior year exacerbations (r = 0.77)2
- Associated with air trapping (p = 0.021)3
- Associated with lung inflammation (p < 0.05)3,4

Majority of AECOPD are associated with a viral or bacterial infection5,6,7
- Transient hyper-responsiveness a feature of pulmonary infection

2. Zanini et al Int J COPD 2015
5. Seemungal et al AJRCCM 2001
7. Sethi et al NEJM 2002
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