Mechanisms of Action & Nuvaira™ Lung Denervation System

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Conflict of interest disclosure

- PneumRx reimbursed the Royal Brompton Hospital and Chelsea & Westminster Hospital for clinical trial expenses (RENEW trial, RENEW Xover, RESET coil randomised trial)
- CSA Medical reimbursed the Royal Brompton Hospital and Chelsea & Westminster Hospital for clinical trial expenses (RejuvenAir trial)
- Nuvaira reimbursed the Royal Brompton Hospital and Chelsea & Westminster Hospital for clinical trial expenses (Airflow trial)
- Uptake medical reimbursed the Royal Brompton Hospital for clinical trial expenses (Step Up trial)
- Pulmonx reimbursed the Royal Brompton Hospital for clinical trial expenses (Liberate trial)
- Boston Scientific, Erbe, Olympus/Keymed, Cook Medical, PneumRx, Medtronic, Immotech, Pulmonx sponsorship to Imperial College for an annual interventional bronchoscopy course
- Consultancy activity for Olympus/Keymed, PneumRx, Medtronic, Nuvaira, Broncus, CSA Medical & Pulmonx sponsorship
By the end of this presentation you should be able to

- Define Targeted Lung Denervation
- Describe the function of the dual-cooled catheter
- List two effects TLD has in the sheep model
- Explain why there is the potential for greater effect in future human studies
Targeted Lung Denervation (TLD): concept and definition

**TLD Concept**

- Treatment site
- Nerves

**TLD Definition**

**Denervation**
- Disrupt parasympathetic nerves to decrease release of acetylcholine

**Lung**
- Decrease smooth muscle tone
- Decrease mucus production

**Targeted**
- Anatomically to only the lung
- To a depth where the nerves are located

Fetal pig lung stained to show airway nerves
TLD designed to decrease airway smooth muscle tone

COPD Before TLD
TLD designed to decrease airway smooth muscle tone

COPD After TLD
Identification and Treatment of Bronchoconstriction Induced by a Vagus Nerve Stimulator Employed for Management of Seizure Disorder*

Jagdeep S. Bijwadia, MD, FCCP, Robert C. Hoch, MD, FCCP, and Donn D. Dexter, MD

We evaluated a 63-year-old woman who developed dyspnea with a sensation of chest tightness that was temporally associated with discharges from a vagus nerve stimulator that had been implanted for the control of intractable seizures. Spirometry demonstrated the development of significant airflow obstruction associated with the firing of the stimulator. Adjustment of the stimulator settings resolved the discharge-associated bronchoconstrictive phenomenon. These findings highlight an important association between vagus nerve stimulators and dyspnea that should be considered in the differential diagnosis of patients with these devices who present with dyspnea and/or chest tightness. The relative importance of vagal stimulation to bronchoconstriction is suggested by the findings.

\[ \text{(CHEST 2005; 127:401–402)} \]

<table>
<thead>
<tr>
<th>Animal</th>
<th>Intervention</th>
<th>Change</th>
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<tbody>
<tr>
<td>Dog</td>
<td>Bilateral cervical vagus cooling</td>
<td>- 22% (R\textsubscript{lung})</td>
</tr>
<tr>
<td>(1962)</td>
<td></td>
<td></td>
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<tr>
<td>Cat</td>
<td>Unilateral cervical sensory vagotomy</td>
<td>- 30% (R\textsubscript{lung})</td>
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<td>(1979)</td>
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<tr>
<td>Cat</td>
<td>Bilateral total cervical vagotomy</td>
<td>- 34% (R\textsubscript{lung})</td>
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<td>(1979)</td>
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<tr>
<td>Sheep</td>
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<td>- 29% (R\textsubscript{lung})</td>
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<td>(1995)</td>
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<tr>
<td>Sheep</td>
<td>Bilateral total cervical vagotomy</td>
<td>- 54% (R\textsubscript{lung})</td>
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<td>(1999)</td>
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<tr>
<td>Human</td>
<td>Bilateral hilar nerve transection</td>
<td>+ 18% MVV</td>
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<td>(1957)</td>
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Evolution of the Nuvaira™ Lung Denervation System
dNerva™ Dual Cooled Catheter

- Catheter Shaft
- Electrode
- Balloon
Effect is targeted to depth with surface cooling
Four step TLD procedure

1. Position
2. Inflate
3. Confirm
4. Activate
TLD procedure animation
Extensive animal testing prior to human use

Studies: 17
Animals: 151
Airways: 295
Activations: 1755
Follow-up: 0, 7, 30, 90, 180, 365, 640 days

Major Findings

• TLD can be performed safely in sheep
• Demonstration of physiologic effect
• Safety profile supports evaluation in human studies
• Decrease in motor innervation durable to two years
• Higher dose produces deeper effect and potential for better efficacy
Figure 21. Normal bronchus distal to treatment site, H&E. Note normal appearance of right mainstem bronchus, imaging in lung, pulmonary vein to right of image, and multiple small nerve branches and bronchial vessels. In particular, note thinness and delicacy of submucosa and peribronchial tissues (compare with treatment induced fibrosis in Figure 1 and 2).
Sustained motor denervation

Motor Axons (ChAT Score)

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<th>ChAT Score</th>
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<tr>
<td>640D</td>
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</table>
Sustained improvement in dynamic airway resistance at 1-yr

![Graph showing dynamic airway resistance improvement over time.](image)

- Treatment @ 365 days (n=4)
- Sham @ 365 days (n=4)

Unpublished Data
Depth of TLD effect can be controlled

Depth of Treatment Effect

Only these 2 tested in early clinical work

Unpublished Data
Conclusions for Targeted Lung Denervation

- Dual-cooled catheter targets tissue heating at depth while protecting the airway surface
- TLD in the healthy sheep model
  - Is safe
  - Produces sustained motor denervation
  - Decreases airway resistance
- Higher energy can produce a deeper effect
- Supports human studies