Mechanism of Action and the Holaira Lung Denervation System

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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**
- Nerves
- Treatment site

**Fetal pig lung stained to show airway 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
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.

*(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% ($R_{lung}$)</td>
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<tr>
<td>Cat</td>
<td>Unilateral cervical sensory vagotomy</td>
<td>- 30% ($R_{lung}$)</td>
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<tr>
<td>Cat</td>
<td>Bilateral total cervical vagotomy</td>
<td>- 34% ($R_{lung}$)</td>
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<tr>
<td>Sheep</td>
<td>Bilateral vagotomy</td>
<td>- 29% ($R_{lung}$)</td>
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<tr>
<td>Sheep</td>
<td>Bilateral total cervical vagotomy</td>
<td>- 54% ($R_{lung}$)</td>
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<tr>
<td>Human</td>
<td>Bilateral hilar nerve transection</td>
<td>+ 18% MVV</td>
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</table>

Evolution of the Holaira™ Lung Denervation System

GEN1

GEN2

Holaira Console

Dual-Cooled Catheter
dNerva™ Dual-Cooled Catheter
Effect is targeted to depth with surface cooling

Tissue Mimicking Gel

Electrode

Balloon
Four step TLD procedure

1. Position
2. Inflate
3. Confirm
4. Activate
TLD Procedure Animation
### Generation 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Animals</th>
<th>Airways</th>
<th>Activations</th>
<th>Follow Up</th>
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**Total** 55 103 934 640 Days

### Generation 2

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**Total** 96 192 821 365 Days

### Major Findings

- Circumferential ablation possible without detrimental airway effects
- TLD can be performed without injury to peribronchial structures
- Decrease in motor innervation durable to 2 years
- TLD improves airway resistance
- Depth of TLD effect tunable by power

- Quadrant electrode decreases procedure time
- Flexible electrode conforms to airway
- Higher dose produces deeper effect and potential for better efficacy
- Safety profile supports evaluation of higher energy doses in AIRFLOW-1
Conclusions

- 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
  - Improves airway resistance
- Higher energy can produce a deeper effect
You too! can invent new technologies in your basement.
None of my neighbors had any idea…