**Targeted lung denervation; an evaluation of power dose effect**

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**Introduction:** Targeted lung denervation (TLD) is a bronchoscopic procedure developed to relieve obstructive lung diseases by disrupting pulmonary vagal afferent inputs.

**Aim:** Define dose effect of TLD.

**Methods:** Following AGLC approval, 28 sheep underwent TLD using a second-generation lung denervation system (Nuvaira, Inc., USA) at multiple powers (30, 34, 36, and 38 W). Each animal's airways underwent bronchoscopic evaluation and semiquantitative histologic evaluation for safety and efficacy at 30 and 90 days post-TLD.

**Results:** There were no animal deaths or significant clinical observations. The effect of TLD was largely undetectable under gross and bronchoscopic inspection except at 38W. Histologically, the targeted treatment zone at all doses consisted of a layer of unaffected tissue encompassing the epithelium, lamina propria, and smooth muscle layers of the airway wall, with a ring of well-organized fibrosis in the outer layer of the airway wall. The fibrosis extended into surrounding adventitia, encasing and obliterating nerve fascicles. Bronchial cartilage effects were limited to the zone and consisted of matrix changes, atrophy, and limited necrosis. Fibroplasia extended up to, but spared, the outer wall of the pulmonary arteries and veins with minimal fibrosis observed in the outer vessel wall at two treatment sites. Tissue proximal and distal to the zone was normal and absent of any treatment effect. Scoring of axonal staining demonstrated similar disruption of nerves at all treatment doses.

**Conclusion:** The current study demonstrates that over the dose range tested, the system safely created a band of fibroplasia surrounding the sheep airway that disrupted axons in bronchial nerve fascicles.

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**Background — Targeted lung denervation (TLD) utilizes radiofrequency (RF) ablation within the main bronchi to disrupt nerve inputs to the lungs**

- Parasympathetic motor nerve tone in COPD
  - Patients with COPD have increased parasympathetic tone in the lungs\(^1\)
  - Anticholinergics decrease parasympathetic tone and reduce resistance to airflow in patients with COPD\(^2,3\)

- Targeted lung denervation (TLD)
  - RF catheter is designed to achieve nerve disruption with parasympathetic tone in COPD
  - TLD using the second generation dNerva\(^\text{TM}\) Catheter is compatible with 3.2mm flexible bronchoscope
  - The Nuvaira\(^\text{TM}\) dNerva\(^\text{TM}\) Dual Cooled RF Catheter:
    - Provides conductive cooling to the airway surface during RF energy delivery
    - Maintains the integrity of the airway mucosa during TLD
    - Targets bronchial nerve fascicles at depth from the airway surface
    - Consists of novel collapsible electrode and cooling balloon
    - Reduced number of activations for complete ablation by half to 4 per bronchi

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**Hypothesis — Increased power dose causes increased tissue effect during TLD with the Nuvaira\(^\text{TM}\) Lung denervation system**

**Methods — 26 sheep underwent circumferential ablation of both main bronchi using a lung denervation system (Nuvaira\(^\text{TM}\), Inc., USA) at multiple powers (30, 34, 36 and 38W)**

- Each bronchus of 26 sheep underwent TLD with the Nuvaira\(^\text{TM}\) System
  - The study was conducted under the guidance of an Institutional Animal Care and Use Committee in accordance with the study facility SOP and Animal Welfare Act of 1996
  - Each bronchus underwent 4 RF activations evenly spaced around the circumference of the airway (quadrants)
  - Animals were survived over to 30 and 90 days and evaluated histologically (n = 48, two sheep experienced early death not related to the device)

**Assessment of Peribronchial Structures**

- Nerve denervation
- Lesion size
- Nerve preservation
- Effect to peribronchial structures

**Assessment of Lung Denervation**

- Graph displays mean normalized depth of effect ± standard error of the mean
- All depths have been normalized to the depth of effect generated by the generation 1 device at 20W
- At 30 days lesion depth is correlated to increase in power (\* indicates p<0.05 vs 38W)

**Effect to peribronchial structures limited to adjacent lung tissue at the treatment site**

- Effects to peribronchial structures are limited to the treatment site
- Evaluation of all peribronchial structures ~1cm above and below the treatment site were normal
- Bronchial epithelium at 30 days, and esophageal tissue were normal upon inspection
- Sustained fibrosis in bronchial wall is an intended effect of treatment to stifle axonal regeneration and was present at all powers and time points
- Graph displays mean normalized depth of effect ± standard error of the mean
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**Conclusion — The current study demonstrates that over the dose range tested, the system safely created a band of fibroplasia surrounding the sheep airway that disrupted axons in bronchial nerve fascicles.**