

**Introduction:** Targeted lung denervation (TLD) is a bronchoscopic procedure delivered using a dual cooled radio frequency ablation catheter. The catheter and denervation system was developed to relieve obstructive airways disease by disrupting pulmonary vagal parasympathetic inputs to the lung while minimizing airway wall effects. The Hering-Breuer inflation reflex (HBR) is a sensory reflex mediated by bronchial vagal sensory axons.

**Aim:** To determine the effect of TLD on Hering-Breuer reflex in healthy adult canine and sheep.

**Methods:** Following IACUC approval, 2 dogs and 2 sheep underwent circumferential ablation of both main bronchi using a lung denervation system (Nuvaira™, Inc., USA). Both dogs were hounds weighing 25 and 39 Kg. Both sheep were mixed breed weighing 45 and 90Kg. The animals underwent evaluation of the HBR prior to and following TLD.

**Results:** All animals demonstrated a normal HBR (cessation of breathing) prior to TLD Therapy. After TLD, vagal denervation of the bronchial branches was clearly demonstrated via interruption of the HBR (continuation of breathing) in the canine model (Figure). The ovine model yielded more variable results with the HBR test due to complications with comfortably anesthetizing the sheep while maintaining spontaneous breathing.

**Conclusion:** TLD successfully disrupts HBR in healthy canines demonstrating a physiological response to lung denervation.

# Demonstration of pulmonary denervation using the Hering-Breuer reflex following Targeted Lung Denervation (TLD)



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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<sup>1</sup>
  - Anticholinergics drugs decrease parasympathetic tone and reduce airflow resistance in COPD patients<sup>2,3</sup>
- Targeted lung denervation (TLD)
  - A novel one time anticholinergic bronchoscopy procedure developed by Nuvaira™ Inc.
  - Utilizes circumferential RF ablation within the main bronchi to disrupt parasympathetic motor nerve input to the lungs

## – Hering-Breuer Reflex (HBR) is triggered to prevent over inflation of the lung and is mediated by pulmonary vagus nerves

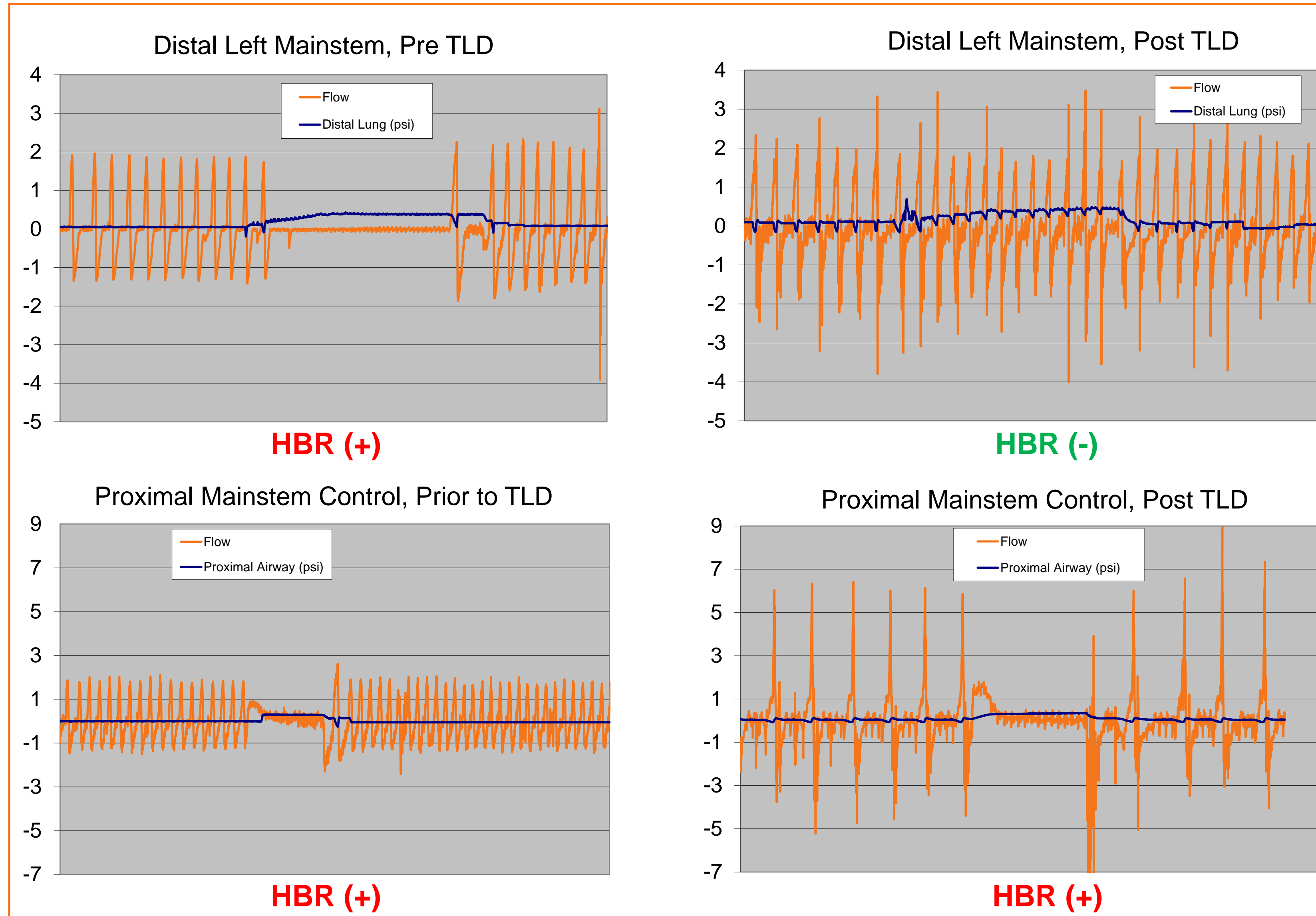
- Pulmonary stretch receptors:
  - Respond to excessive stretching of the lung during large inspirations
  - Send action potentials through large myelinated fibers of the vagus nerve to the brain stem which inhibit inspiration
- TLD using the Nuvaira™ Catheter is designed to disrupt vagus nerve inputs to lung
  - Following the TLD procedure it is expected that the Hering-Breuer reflex would be abolished in regions of the lung distal to the treatment.

## Hypothesis – TLD with the Nuvaira™ Lung Denervation System disrupts pulmonary parasympathetic nerves in locations distal to TLD treatment as demonstrated by loss of HBR.

## Methods – 2 dogs and 2 sheep underwent circumferential ablation of both main bronchi using a lung denervation system (Nuvaira™, Inc., USA).

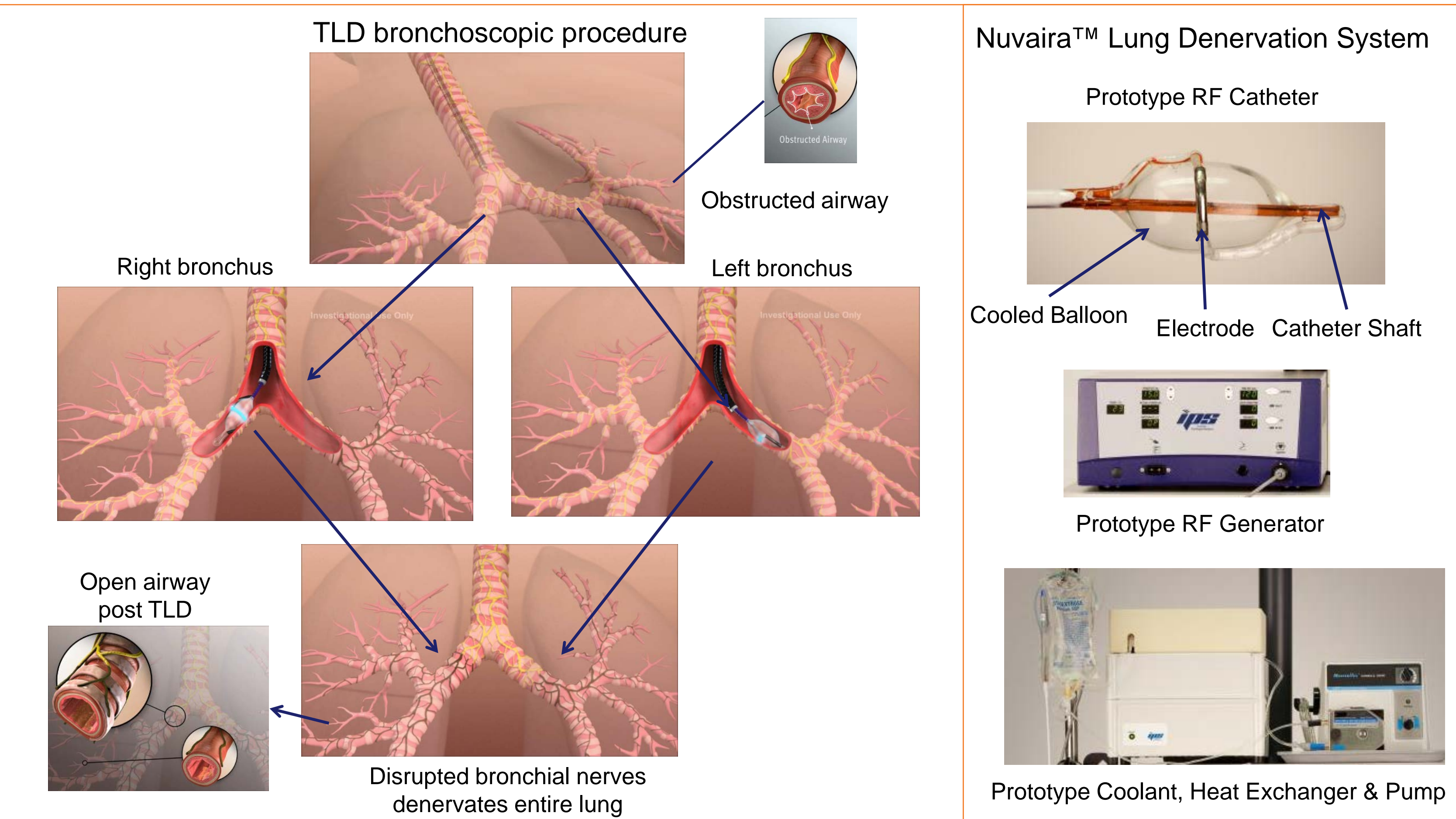
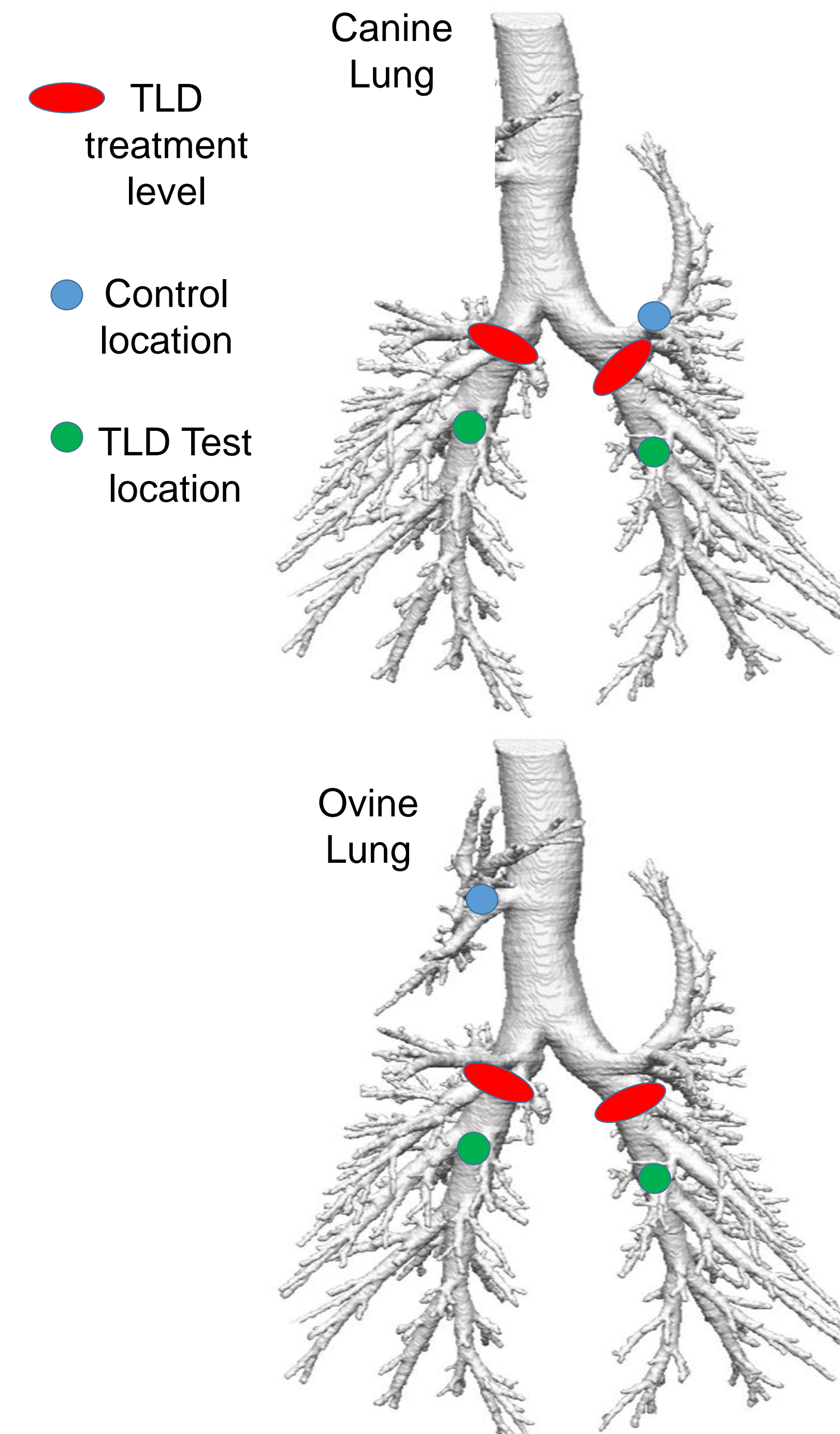
- Each bronchus of 2 sheep and 2 dogs underwent TLD with the Nuvaira™ System
  - The study was conducted under the guidance of an Institutional Animal Care and Use Committee in accordance with the study facility SOP and Animal Welfare Act of 1966
  - Each bronchus (n = 8) underwent 8 sequential RF activations evenly spaced around the circumference of the airway (octants)
  - Prior to, acutely following, and 7 days following TLD therapy, each was tested for presence or absence of the HBR in locations in the lung proximal and distal to site of denervation.
  - Hering-Breuer Reflex was measured with a custom built test system described below.

## Results – The vagal mediated Hering-Breuer response was abolished in locations in the lung distal to TLD treatment.



## Hering-Breuer Reflex (HBR) test

- HBR was used to assess lung denervation following TLD.
- Whole lung proximal to the treatment site in canine and the accessory right upper lobe in sheep was used as control. These locations are not denervated by the TLD procedure and confirm reflex is active.
- Functionality of the HBR was assessed in the proximal whole lung (canine)/accessory right upper lobe (ovine), distal left and right mainstem bronchi prior to and following TLD. One animals from each species was survived for 7 days and the HBR evaluation was performed again.
- Animals were sedated but spontaneously breathing.
- A triple lumen, balloon tipped catheter was placed in region of interest, and balloon inflated to occlude and isolate region of interest
- Flow in and out of the endotracheal tube was measured and with the balloon inflated, the lung distal to the balloon was pressurized
- Cessation of respiratory flow represents a positive HBR and an intact vagus nerve to the occluded and pressurized portion of the lung. **HBR(+)**
- Continuation of respiratory flow represents an absent HBR and a loss of vagus innervation to the occluded lung. **HBR(-)**



References –  
<sup>1</sup>Undem B. and Kollarik M. Proc Am Thor Soc 2005; 2: 355-360.  
<sup>2</sup>Belmonte K. Proc Am Thor Soc 2005; 2: 297-305.  
<sup>3</sup>Qaseem A, Wilt T, Weinberger S, et al. Ann Intern Med. 2011; 155: 179-91.  
<sup>4</sup>Merryn H. Tawhai et al. J Appl Physiol 2004;97:2310-2321

- Table displays the HBR results for each animal
- Sustained effect 7days post treatment in canine
- HBR was abolished acutely in all animals except animal 3
- Single lung sustained effect in ovine and diminished effect in the right lobe
- Animal 3 Low power treatment

Animal ID	Model	Survival (d)	Lung	Power (W)	HBR		
					Day 0 Pre	Day 0 Post	Day 7 Pre-Sac
1	Canine	0	R	25	+	-	NA
			L	25	+	-	NA
			C	NA	+	+	NA
2	Canine	7	R	15	+	-	-
			L	25	+	-	-
			C	NA	+	+	+
3	Ovine	0	R	15	+	+	NA
			L	10	+	+	NA
			C	NA	+	+	NA
4	Ovine	7	R	25	+	-	+/-
			L	25	+	-	-
			C	NA	+	+	+

**Conclusion – TLD successfully disrupts HBR in healthy canines demonstrating a physiological response to lung denervation.**