Introduction: Targeted lung denervation (TLD) is a bronchoscopic procedure developed to relieve obstructive airways disease by disrupting pulmonary parasympathetic inputs to the lung. A denervation system and novel radiofrequency ablation catheter with dual cooled design was developed to facilitate ablation of bronchial branches of the vagal trunk while minimizing airway wall effects.

Aim: To determine the effect of lung denervation on pulmonary resistance in healthy sheep.

Methods: Following IACUC approval, 3 sheep underwent circumferential ablation of both main bronchi using a lung denervation system (NuvairaTM, Inc., USA). All sheep were mixed breed and weighed 47-51 Kg. Prior to and following TLD therapy, each animal underwent a series of pulmonary resistance measurements using a custom built forced oscillometry system. Atropine was utilized as a positive control to demonstrate bronchodilation prior to TLD.

Results: The effect of TLD therapy was evident in all three animals. On average, the airway resistance decreased by 27% (1.34 cmH2O/(L/s)) and 30% (1.28 cmH2O/(L/s)) in response to the peak effect of atropine and post-TLD therapy, respectively. The effect from TLD was maintained at 90 min post treatment while the effect of atropine resolved over the same time frame.

Conclusion: Healthy sheep subjected to TLD demonstrated decreased airway resistance comparable to the peak effect of atropine.

Improved pulmonary resistance in health sheep following Targeted Lung Denervation (TLD)

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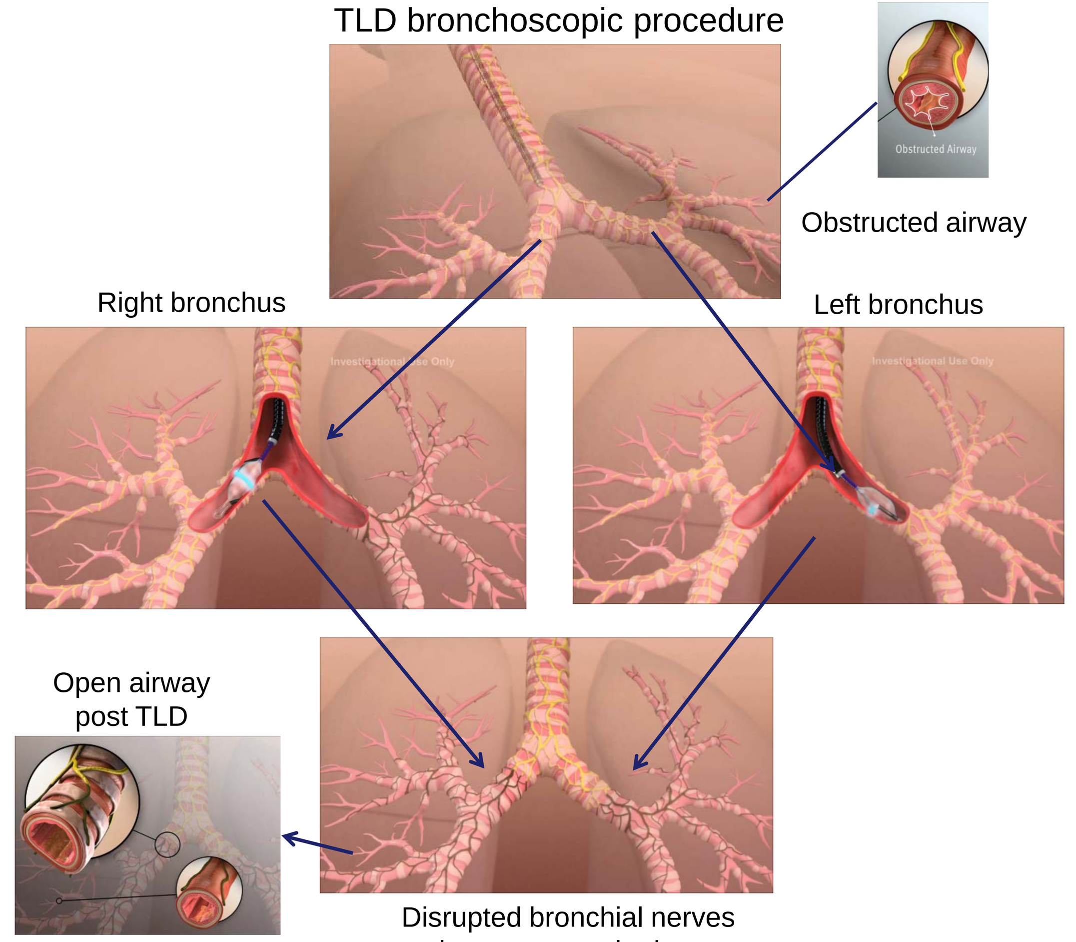
Background – Targeted lung denervation (TLD) utilizes radiofrequency (RF) ablation within the main bronchi to disrupt nerve inputs to the lungs

- Parasympathetic motor nerve tone in COPD
  - Patients with COPD have increased parasympathetic tone in the lungs[1]
  - Anticholinergics decrease parasympathetic tone and reduce resistance to airflow in patients with COPD[2,3]
- Targeted lung denervation (TLD)
  - A novel one time anticholinergic bronchoscopy procedure developed by NuvairaTM Inc.
  - Utilizes circumferential RF ablation within the main bronchi to disrupt parasympathetic motor nerve input to the lungs

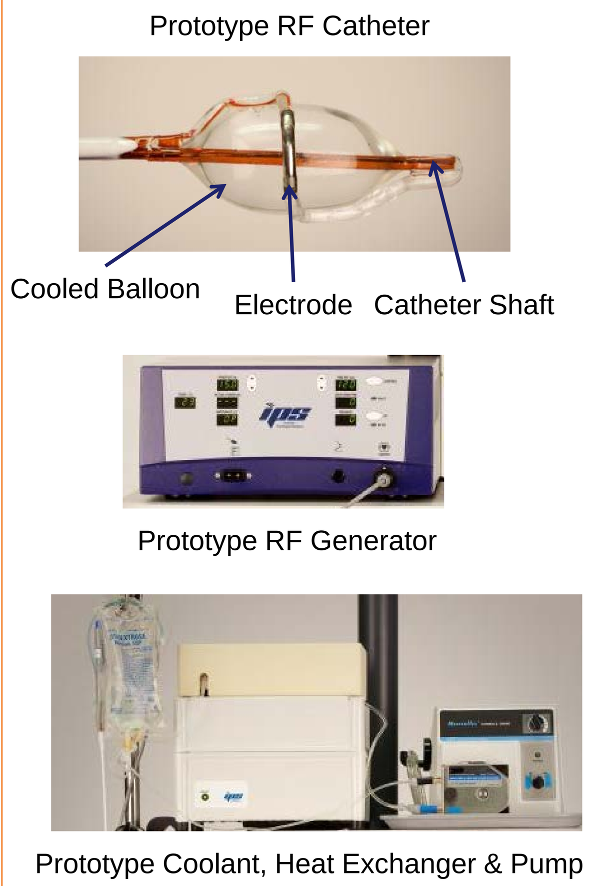
– RF catheter is designed to achieve nerve disruption with minimal effects to the airway surface and peribronchial structures

- The NuvairaTM 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
- TLD using the NuvairaTM Catheter is designed to minimize ablation effects to non targeted surrounding lung tissue

TLD bronchoscopic procedure



Nuvaira™ Lung Denervation System



References –

[1]Undem B. and Kollarik M. The Role of Vagal Afferent Nerves in Chronic Obstructive Pulmonary Disease. Proc Am Thor Soc 2005; **2**: 355-360.

[2] Belmonte K. Cholinergic Pathways in the Lungs and Anticholinergic Therapy for Chronic Obstructive Pulmonary Disease. Proc Am Thor Soc 2005; **2**: 297-305.

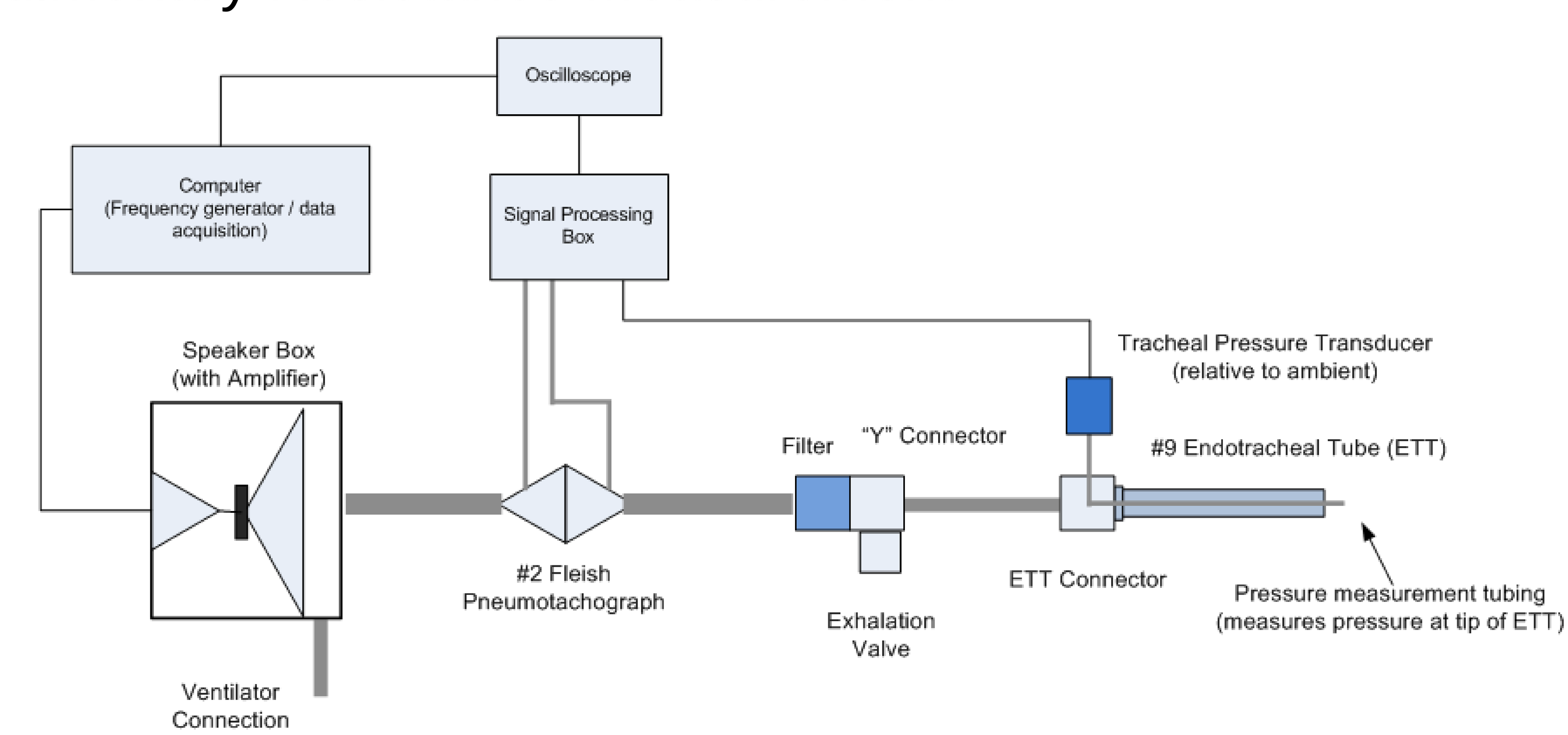
[3] Qaseem A, Wilt T, Weinberger S, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: A clinical practice Guideline update from the ACP, ACCP, ATS and ERS. *Ann intern Med.* 2011; **155**: 179-91.

Hypothesis – TLD with the NuvairaTM Lung Denervation System in sheep disrupts parasympathetic input to the lungs decreasing pulmonary resistance.

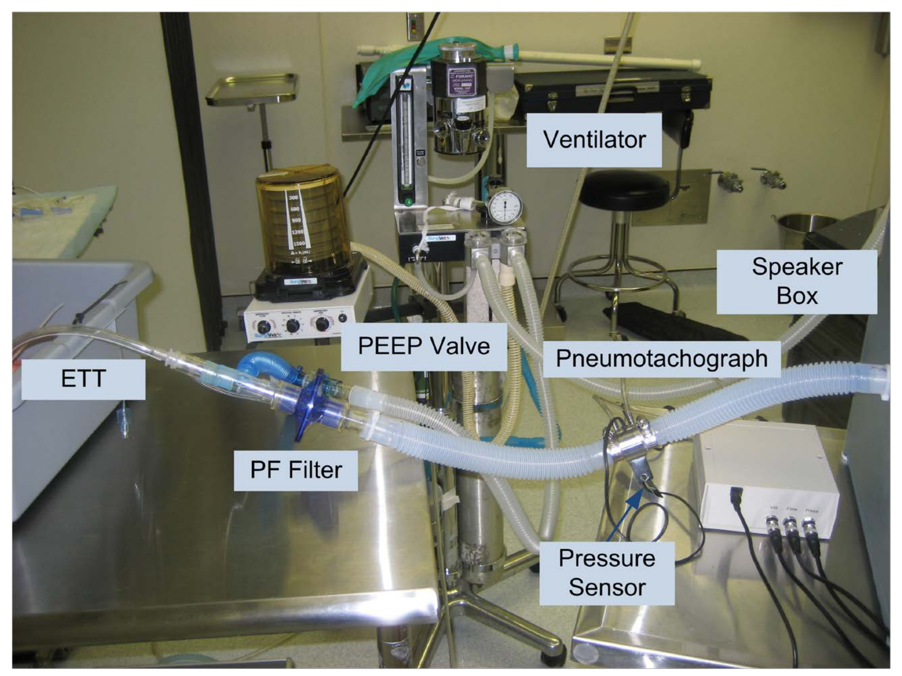
Methods – 3 sheep underwent circumferential ablation of both main bronchi using a lung denervation system (NuvairaTM, Inc., USA).

- Each bronchus of 3 sheep underwent TLD with the NuvairaTM 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 =6) underwent 8 sequential RF activations evenly spaced around the circumference of the airway (octants)
  - Prior to and following TLD therapy, each animal underwent a series of pulmonary resistance measurements using a custom built forced oscillometry system.
  - Atropine was utilized as a positive control to demonstrate bronchodilation prior to TLD.

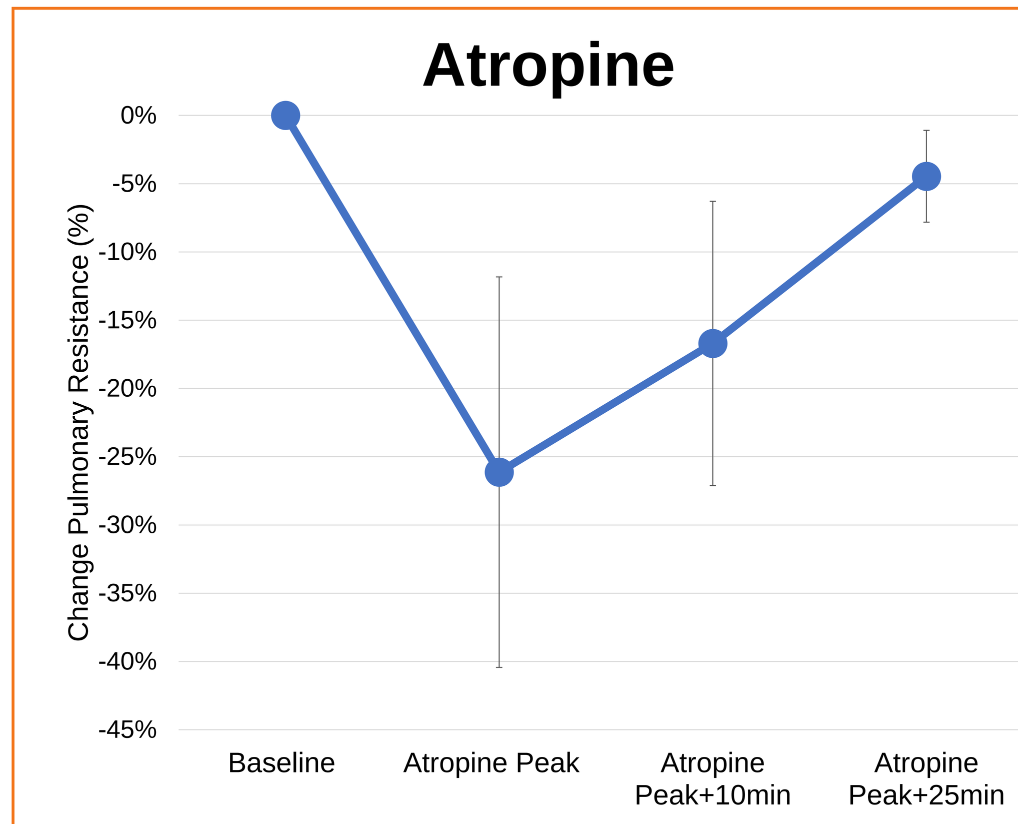
Pulmonary Resistance Measurement



- A forced oscillation system to measure the pulmonary resistance was assembled
- Breathing of the animal was controlled by ventilator set to 10-15 bpm, VT 0.5 L, Pinsp = 10 cm H2O, and PEEP = 5cm H2O
- A 5Hz pressure wave was generated by a custom speaker box and superimposed on the animals' controlled breathing.
- Air flow was measured by a calibrated, heated pneumotachograph, and pressure was measured by a pressure transducer
- Pneumotachograph and pressure transducer output were displayed on an oscilloscope, 5 Hz component isolated, and airway impedance determined by dividing airflow by pressure

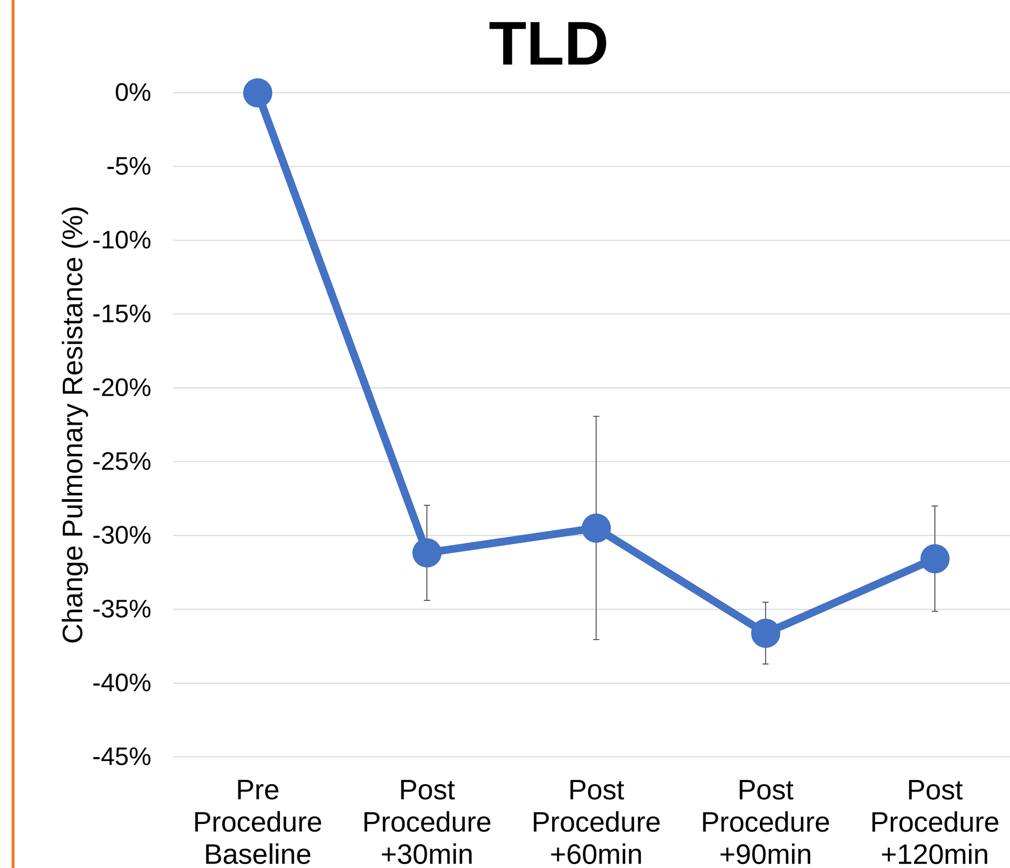


Results – Atropine caused a transient 26% peak reduction in pulmonary resistance that normalized after 25min



- Graph displays the % change in pulmonary resistance at baseline, atropine peak, 10 min after atropine peak, and 25 min after atropine peak
- Atropine is a known anti-cholinergic that has been shown to cause bronchodilation and decrease airway resistance.
- Atropine was delivered intravenous at a dose of 5 – 10 mg/min
- Systemic delivery of atropine caused a transient reduction in pulmonary resistance with a 26% peak effect.
- 25min following the peak effect pulmonary resistance was normal. The short duration of effect is related to atropinase in sheep that rapidly breaks down atropine enabling them to eat nightshade and Jimson weed in the wild.

TLD using the lung denervation system caused a sustained >30% reduction in pulmonary resistance in treated animals



- Graph displays the % change in pulmonary resistance at baseline, 30 min post TLD, 60 min post TLD, 90 min post TLD and 120 min post TLD
- TLD disrupts the parasympathetic input to lungs and thus is intended to decrease cholinergic tone and induce bronchodilation.
- 30 min following the TLD procedure the pulmonary resistance of the treated lungs decreased on average by 31%.
- Unlike atropine, bronchodilation induced by TLD was sustained post treatment due to permanent disruption of the parasympathetic nerves.
- Pulmonary resistance was not measured beyond 120 min post TLD procedure.

Conclusion – TLD treatment induces bronchodilation through nerve disruption that is sustained and comparable in magnitude to the anticholinergic effect produced by atropine.