

Introduction: Targeted lung denervation (TLD) is a bronchoscopic procedure developed to relieve obstructive airways disease by disrupting pulmonary vagal parasympathetic inputs.

Aim: Define dose effect of TLD.

Methods: Following IACUC approval, 26 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. This 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.

Targeted lung denervation; an evaluation of power dose effect



P.J. Johnson¹, M.L. Mayse¹, K.T. Rouw¹

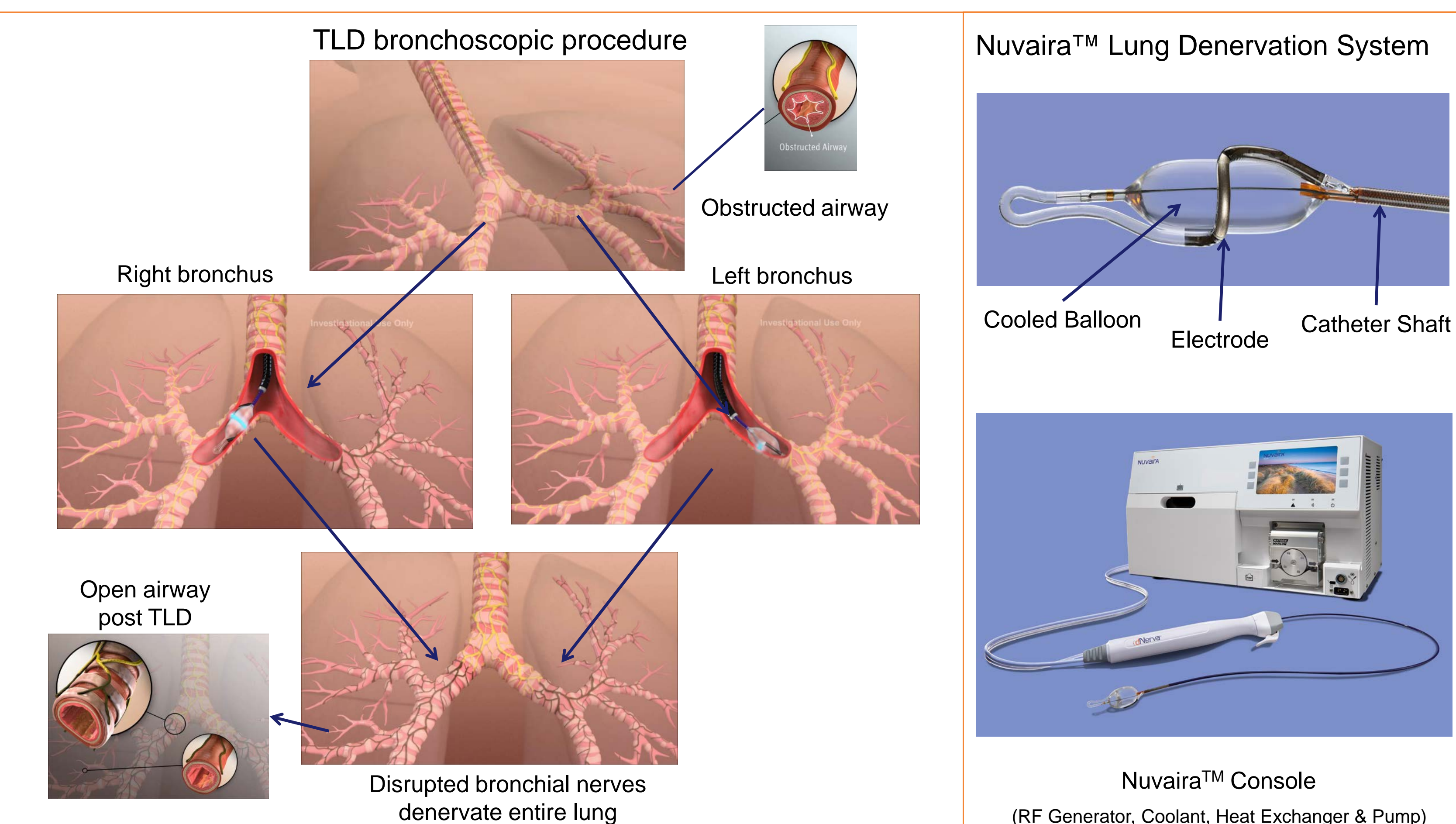
¹Nuvaira, Inc., Minneapolis, MN, USA

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 lungs¹
 - 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 Nuvaira 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 Nuvaira™ dNerva™ 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 second generation dNerva™ Catheter is compatible with 3.2mm flexible bronchoscope
 - Consists of novel collapsible electrode and cooling balloon
 - Reduced number of activations for complete ablation by half to 4 per bronchi



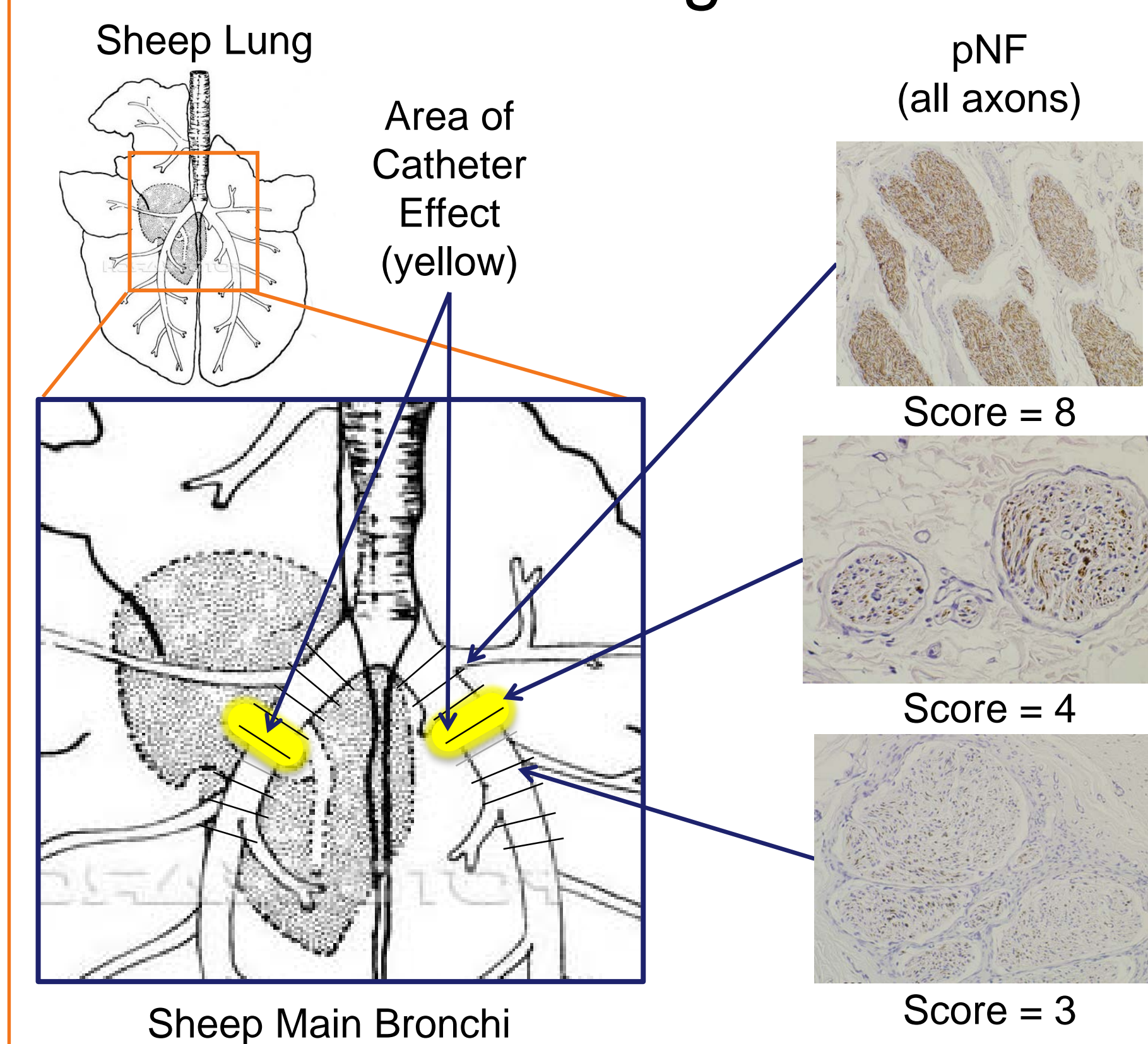
References –
¹Undem B. and Kollarik M. The Role of Vagal Afferent Nerves in Chronic Obstructive Pulmonary Disease. *Proc Am Thor Soc* 2005; **2**: 355-360.
²Belmonte K. Cholinergic Pathways in the Lungs and Anticholinergic Therapy for Chronic Obstructive Pulmonary Disease. *Proc Am Thor Soc* 2005; **2**: 297-305.
³Qaseem 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 – Increased power dose causes increased tissue effect during TLD with the Nuvaira™ lung denervation system

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

- Each bronchus of 26 sheep 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 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)
 - Lesion size
 - Nerve denervation
 - Affect to peribronchial structures

Assessment of Lung Denervation



Axon Staining

- Anti-pan neurofilament (pNF)
 - 30 day time point only
 - Stains all axons, compared to upstream

Assessment location and score

- Each nerve fascicle larger than 50µm in diameter at
 - Treatment site: pNF
 - Proximal (~1cm): pNF
 - Distal (~1cm): pNF
- 0-10 semi-quantitative score
 - 0: no staining, 10: 100% staining.

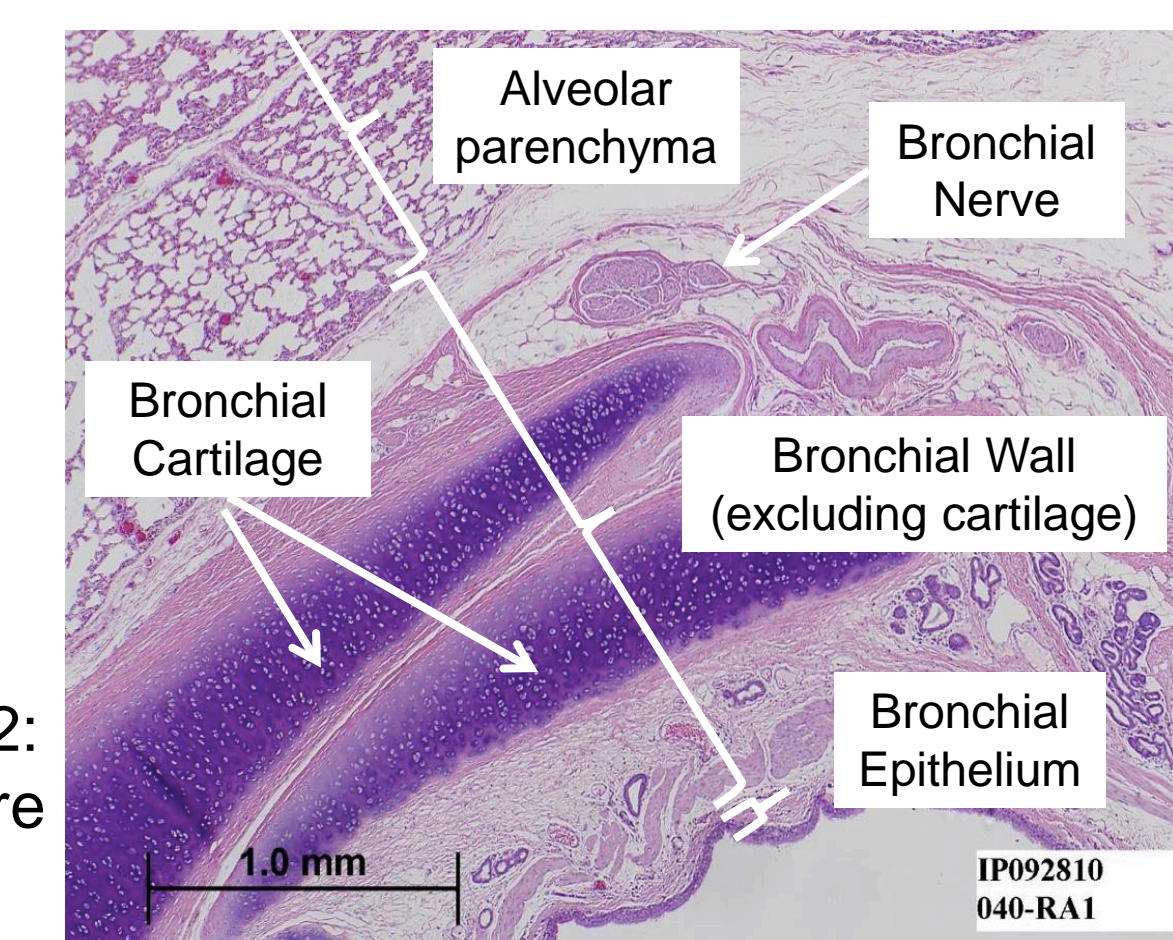
Assessment of Peribronchial Structures

Structures:

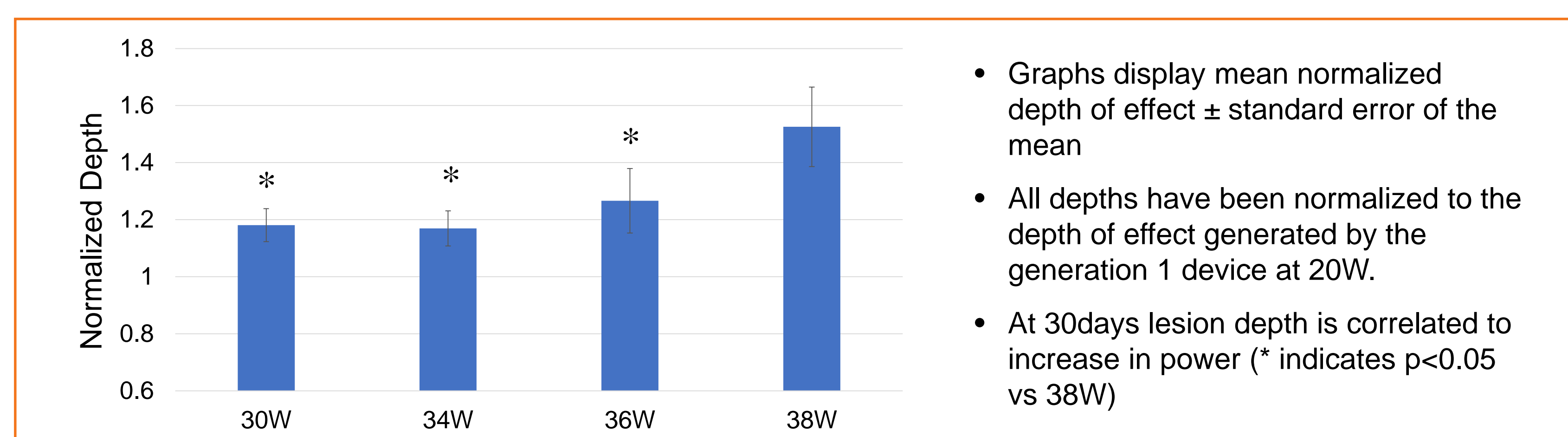
- Bronchial epithelium
- Bronchial wall
 - Lamina propria, smooth muscle, submucosa, and adventitial layer
- Bronchial cartilage
- Alveolar parenchyma
- Blood vessels

Location/Assessment:

- Treatment site
- Proximal (~1cm)
- Distal (~1cm)
- 0-4 semi-quantitative score
 - 0: no change, 1: minimal, 2: mild, 3: moderate, 4: severe

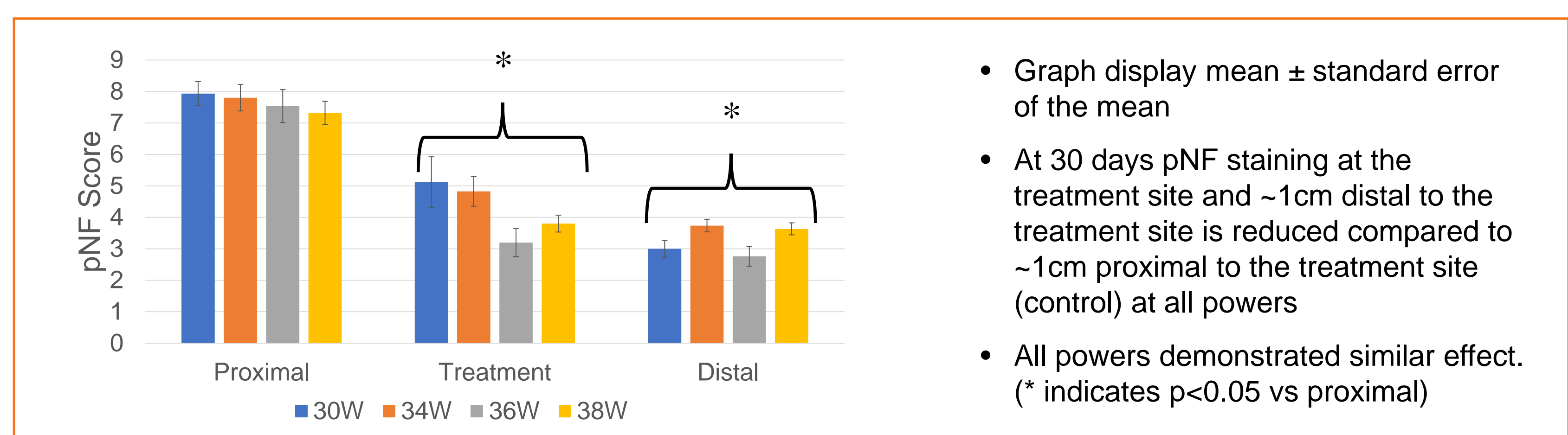


Results – Increased power correlates to increased lesion depth



- Graphs display 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 30days lesion depth is correlated to increase in power (* indicates p<0.05 vs 38W)

Axonal staining (pNF) was decreased 60% at 30 days after TLD



- Graph display mean ± standard error of the mean
- At 30 days pNF staining at the treatment site and ~1cm distal to the treatment site is reduced compared to ~1cm proximal to the treatment site (control) at all powers
- All powers demonstrated similar effect. (* indicates p<0.05 vs proximal)

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 90 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
- Extent of tissue effect on bronchial epithelium, bronchial wall fibrosis, cartilage ring necrosis, volume of adjacent lung parenchyma affected, and blood vessel tunica media remodeling from TLD followed a dose dependent trend at the 30 day time point
- Damage to airway cartilage was limited to the area directly below the treatment site and did not cause significant changes to airway architecture.
- Effect on major blood vessels was limited to the treatment site and was largely normal at 90 days.

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.