

## Targeted lung denervation for chronic obstructive pulmonary disease

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We recently performed the first-in-human study investigating bronchoscopic radio-frequent ablation of the parasympathetic pulmonary nerves in patients. This new bronchoscopic minor-invasive therapy called “targeted lung denervation” (TLD) is a potential future treatment option for patients with advanced COPD. The first results show that TLD in patients with COPD is feasible, safe and has clinical benefit which appears both durable and dose dependent [ref 1].

Targeted lung denervation (TLD) is a novel bronchoscopic therapy that ablates the parasympathetic innervation of the lungs and has a similar proposed mechanism of action to anticholinergic drugs. TLD therapy is delivered via a dual-cooled radiofrequency (RF) catheter (Holaira, Inc., Minneapolis, MN, USA) (figure 1) designed to target tissue heating at depth thereby producing a narrow band of ablation around the main bronchi while minimizing effects to the inner surface of the airway.

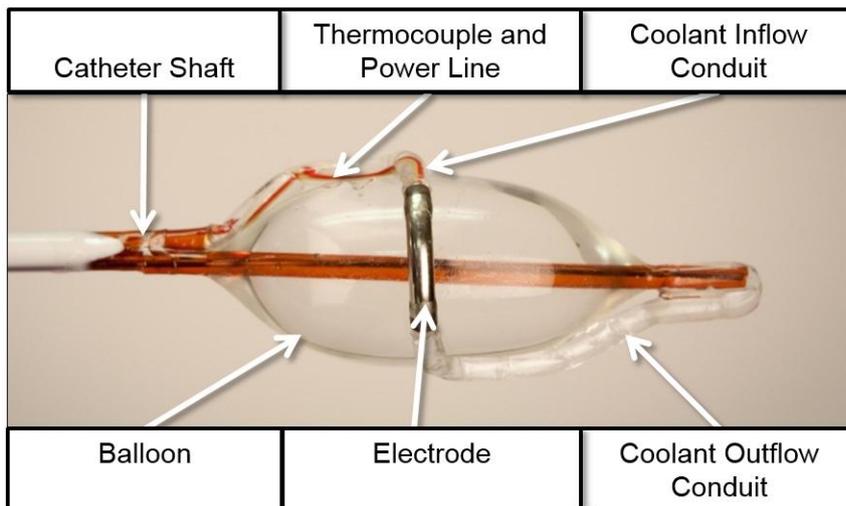


Figure 1 - dual-cooled radiofrequency catheter

As RF current passes from the electrode through the airway and surrounding tissues, these tissues are heated. Coolant continuously circulated through the electrode and balloon removes heat from the surface of the airway wall. The net effect is targeted tissue ablation at depth with minimal heating and damage of the inner surface of the airway.

This targeted tissue ablation is intended to disrupt motor axons within bronchial nerve branches running along the outside of the main bronchi, thereby blocking parasympathetic signaling to the lungs and decreasing neuronal release of acetylcholine. This decrease in acetylcholine reduces airway obstruction in the whole lung by decreasing smooth muscle tone and mucous production (figure 2).

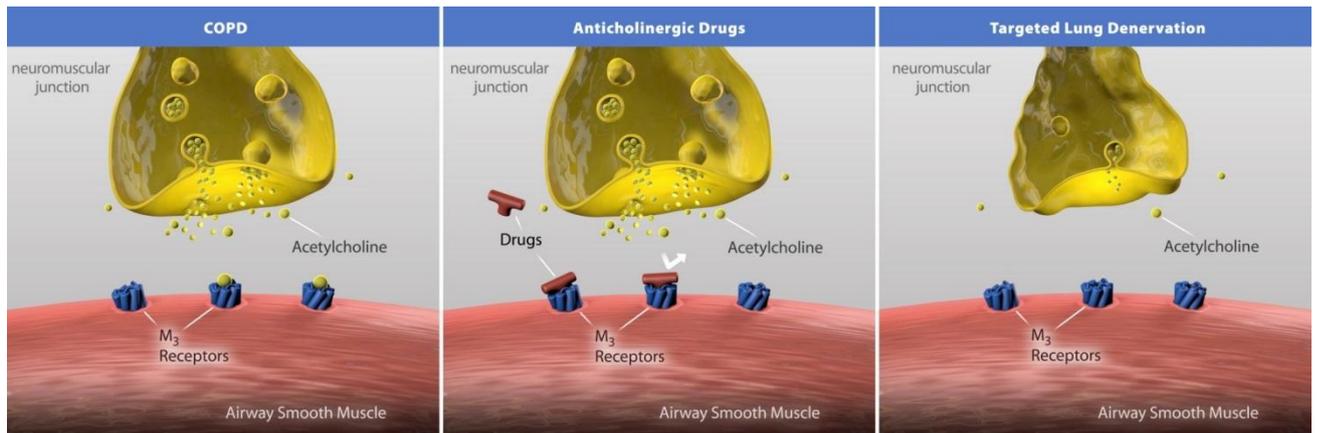


Figure 2- Targeted Lung Denervation is intended to block parasympathetic signaling and reduce acetylcholine release from the nerve endings.

In a first-in-human study we investigated the safety and feasibility of TLD therapy using two energy doses (20 and 15 watts) in patients with moderate to severe COPD. In a non-randomized, prospective study COPD patients were included with a post-bronchodilator FEV<sub>1</sub> of 30-60% of predicted normal values and with a 15% or greater relative increase in FEV<sub>1</sub> following inhalation of 80µg ipratropium bromide.

### TLD-Treatment procedure

Due to the construction of this first generation device, procedures were performed via rigid bronchoscopy under general anesthesia in 2 sequential bronchoscopies (figure 3). The dual-cooled catheter was placed through the rigid bronchoscope and a flexible bronchoscope placed beside it for visualization. The electrode was placed and activated in up to 8 rotational positions per bronchus to achieve complete circumferential treatment. Total balloon inflation times were approximately 3 minutes per activation. Bronchoscopic and fluoroscopic visualization was used to guide in electrode positioning throughout treatment (figure 3).

Figure 3 – TLD Procedure room

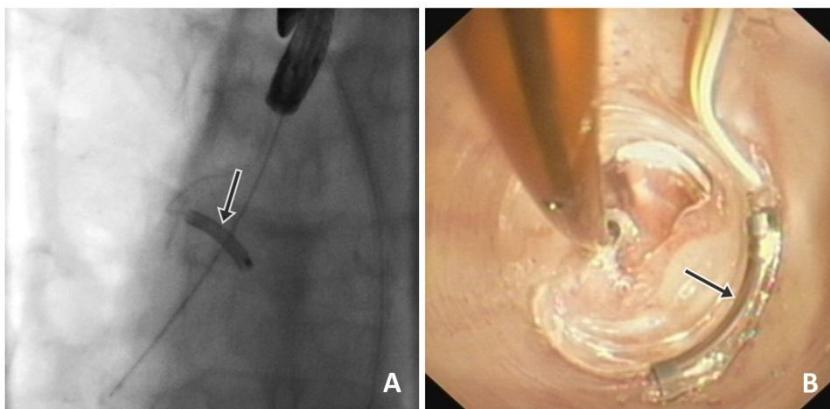


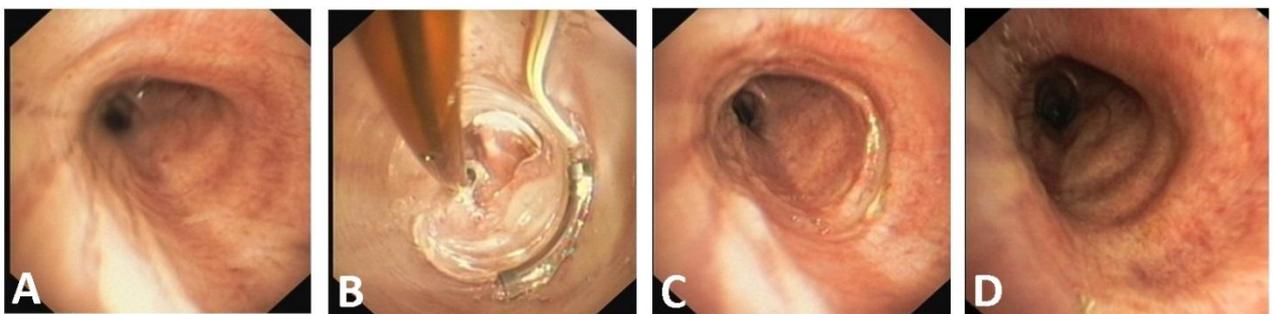
Figure 4: Fluoroscopic view (A) and Bronchoscopic view (B) of the electrode during the procedure. The electrode is indicated by the arrow.

## Results

Twelve patients were included in the 20watt cohort and an additional 10 patients were included as part of the 15watt cohort. Baseline characteristics were similar between the two cohorts. The primary safety endpoint was achieved in 100% (11/11) in the 20watt cohort and 90% (9/10) in the 15watt cohort. The one subject that failed to meet the endpoint had a sustained decline in lung function over time.

The RF energy applied to the airway wall resulted in local asymptomatic airway blanching, which resolved at the 3 month follow-up bronchoscopy in all 10 of the 15watt patients, and in 8 of the 11- 20watt patients with long-term follow up (figure 5).

*Figure 5 - Bronchoscopic confirmation of airway healing after TLD: (A) Left main bronchus pre-treatment (B) During treatment (C) Immediately post-Treatment (D) 3 month follow-up.*



In the 20watt group, one patient had a superficial tissue defect at the first treatment site seen at 30 days, a second patient had a small 1.5 mm perforation through the thin tissue of the main carina also discovered at 30 days, and the third patient had a superficial tissue defect at the initial treatment site just distal to the main carina, as well as a 4 mm granuloma at the second treatment site.

The procedure was feasible in all cases and technical success was 98%, with 326 of 332 expected treatment sites able to be treated. No device related adverse events occurred during the procedure. The results of FEV<sub>1</sub> (% relative change), FVC, cycle ergometry endurance and SGRQ at each time point assessed are shown in figure 6.

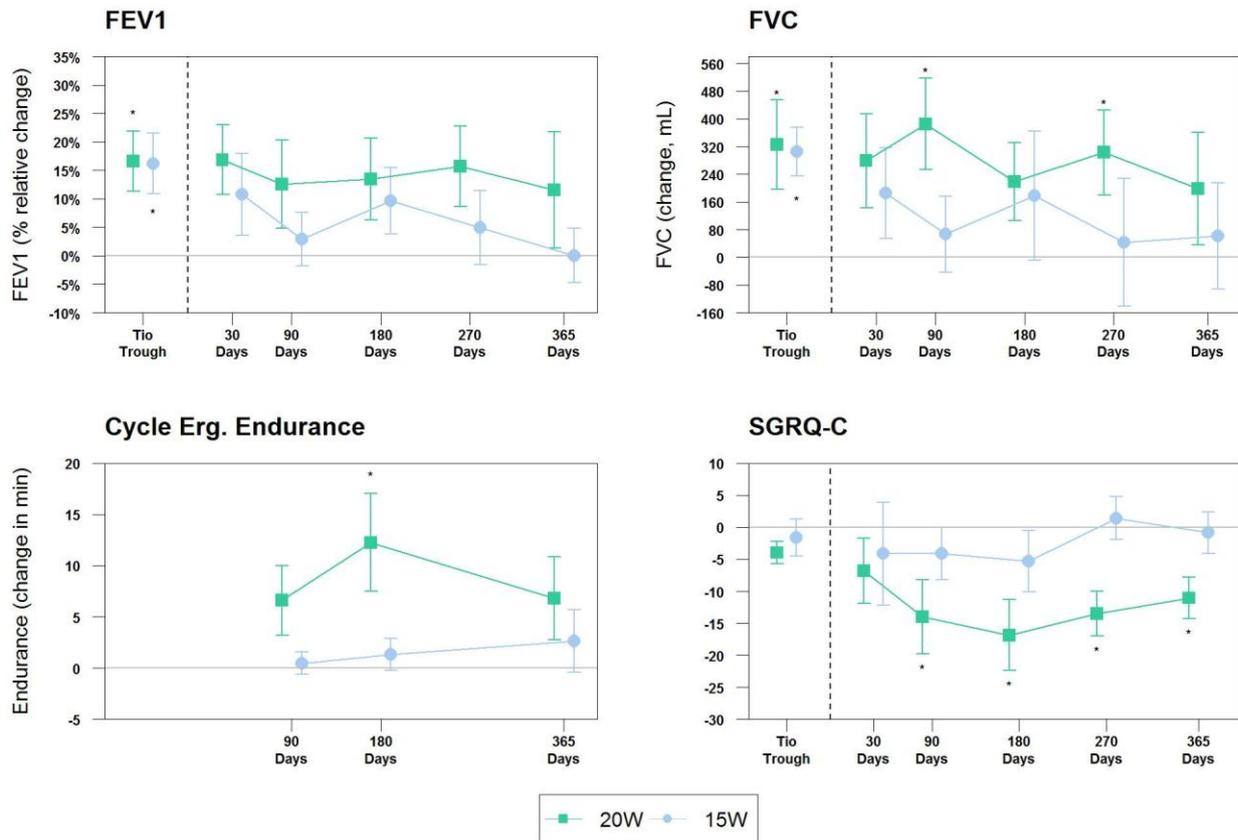


Figure 6: Secondary efficacy endpoints. Data represented as mean. Error bars represent standard error of the mean. \* $p < 0.05$  compared to baseline. FEV<sub>1</sub>: Forced Expiratory Volume in 1 second. FVC: Forced Vital Capacity. Cycle Erg. Endurance: Cycle Ergometry Endurance. SGRQ: St. George's Respiratory Questionnaire

## Discussion

This first-in-human clinical trial evaluated the novel “targeted lung denervation” (TLD) therapy, designed to ablate the parasympathetic pulmonary nerves surrounding the main bronchi thereby decreasing bronchomotor tone in patients with COPD. This study demonstrated TLD to be feasible, safe, and potentially beneficial. The primary endpoint was met in 95% of patients and technical success was 98%. Tendency toward improvements in lung function, exercise capacity, and HRQL were observed in the 20watt cohort. These improvements tended to be larger than those seen in the 15watt cohort.

TLD has the potential to overcome many of the limitations of inhaled drugs for the treatment of COPD. First, TLD may eliminate inhaler compliance issues for the 63% of new tiotropium users who discontinue treatment after 1 year. Second, TLD would not be subject to the peak and trough variations seen with drugs. Third, TLD may eliminate variable regional drug delivery and deposition in patients with obstructive lung disease by ablating the nerves that travel throughout the bronchial tree independent of regional airflow obstruction. Fourth, by interfering with parasympathetic nerve derived acetylcholine by two different mechanisms, the combination of TLD + inhaled anticholinergic drugs, as suggested by figure 7, may have a synergistic effect that results in a reduction in airway obstruction and mucus production, as well as inhibition of local airway inflammation induced by non-neural muscarinic action.

In this paper we introduced TLD, a novel bronchoscopic treatment concept for symptomatic patients suffering from COPD. Based on the concept of ablating parasympathetic pulmonary

nerves, TLD was shown to be feasible, safe, and potentially clinically effective. The beneficial effects appear durable, dose dependent and potentially additive to inhaled anticholinergics.

Further investigation and progressive product development is currently underway. A new catheter and RF system have been developed, allowing a single outpatient 45 mins procedure (figure 7). This system will be tested and used in the “AIRFLOW-1 trial” (NCT02058459): A Sequential 2-Phase Multicenter, Randomized Study to Optimize Dose Selection and Evaluate Safety After Treatment with the Holaira™ Lung Denervation System in Patients with Moderate to Severe COPD.



*Figure 7. The new generation TLD system*

**Reference:** Slebos DJ, Klooster K, Koegelenberg CF, Theron J, Styen D, Valipour A, Mayse M, Bolliger CT. Targeted lung denervation for moderate to severe COPD: a pilot study. *Thorax*. 2015 Mar 4. [Epub ahead of print]