Randomized Sham Controlled Trial of Targeted Lung Denervation in Patients with COPD (AIRFLOW-3)

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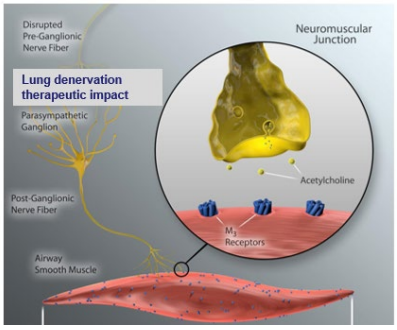
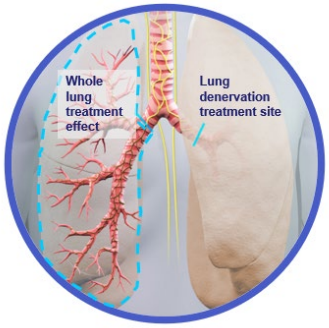
DOI: https://doi.org/10.1164/rccm.202502-0404OC

Background and Intervention

COPD patients who remain symptomatic despite optimal medical therapy have increased risk of COPD exacerbation, which worsens clinical prognosis and increases risk of hospitalization. Autonomic nervous system dysregulation in COPD drives excessive bronchoconstriction and hyperinflation; blunting parasympathetic nerve impact is a focus of routine pharmacotherapy (i.e. inhaled LAMA and LABA).





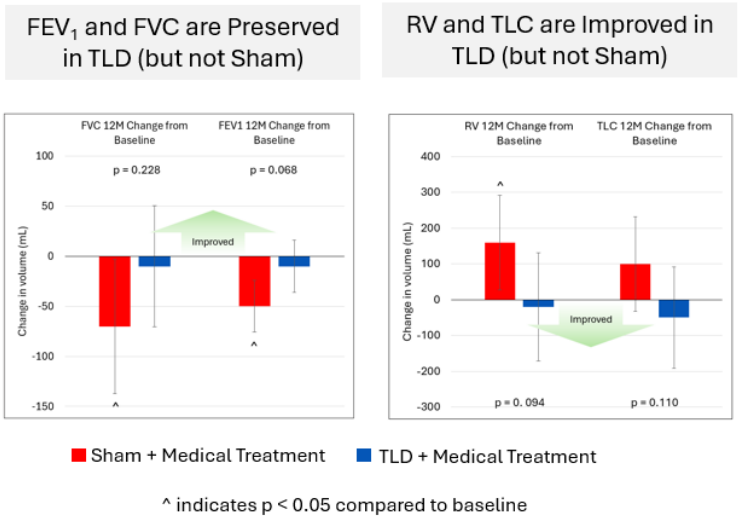
Lung denervation is a single outpatient procedure to ablate pulmonary nerves at the mainstem bronchi to reduce the clinical consequences of neural hyperactivity.

Clinical Trial

388 COPD patients with moderate to very severe airflow obstruction (FEV_1 25-80% pred.) and prior year documented exacerbations (≥2 moderate or ≥1 severe) were double-blind randomized 1:1 to TLD (dNerva® lung denervation) or sham procedure while remaining on optimal medical treatment (92% triple therapy) for one year of follow-up at 32 sites (US, UK, EU). The primary endpoint was time-to-first moderate or severe exacerbation.

Results

Figure 1

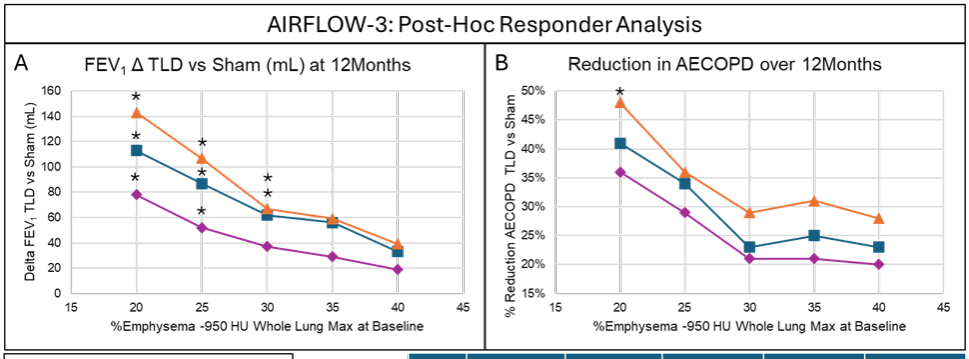


The primary endpoint was not statistically different between the TLD and sham groups (HR 1.268; CI 0.988 to 1.628 per ITT analysis). Between-group improvements in lung function and dyspnea led to post-hoc identification of a TLD responder profile consistent with lung denervation mechanistic impact in obstructive lung disease (Figure 1).

Patients with lung hyperinflation driven by airways dominant pathology (high RV despite minimal emphysema) had significant improvements in lung function, exacerbation rate reduction, and dyspnea

(Figure 2). No other baseline characteristics (i.e. BEC, age, BMI, site or region) significantly impacted post-hoc outcomes.

Figure 2



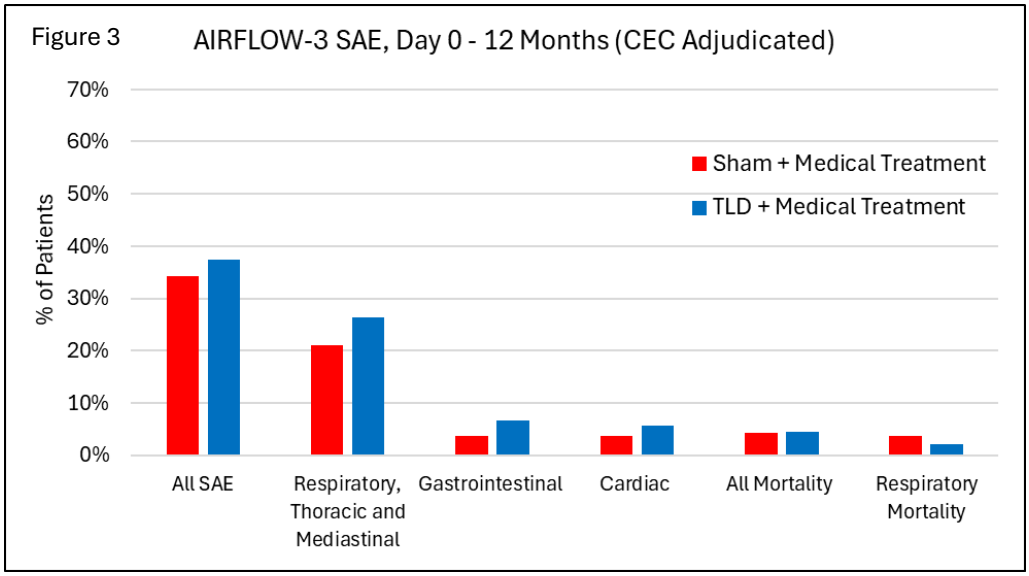
	≤20% Emphysema		≤25% Emphysema		≤30% Emphysema		≤35% Emphysema		≤40% Emphysema	
n	TLD	Sham	TLD	Sham	TLD	Sham	TLD	Sham	TLD	Sham
≥205%	25	22	34	32	45	46	53	55	62	59
≥175%	44	41	55	53	70	71	55	53	40	38
≥155%	48	53	69	68	89	88	106	101	118	114

HIGHER baseline RV and LOWER baseline emphysema predict GREATER magnitude of one-year improvement in TLD vs. Sham patients.

Safety

The safety profile through one year of follow-up was similar between TLD and sham groups (Figure 3). Higher rates of peri-procedural (0-90 day) respiratory Severe Adverse Events (SAE) in the TLD group were improved with the addition of esophageal cooling mid-trial, which also eliminated the risk of broncho-esophageal fistula from RF energy.

Figure 3



Limitations, Conclusions and Remaining Questions

AIRFLOW-3 was conducted through the SARS-COV-19 pandemic which impacted reported rates of COPD exacerbations worldwide.

Preservation of lung function and improved dyspnea following TLD was observed in the ITT analysis. These findings led to a post-hoc analysis that identified an airways-dominant TLD treatment responder phenotype.

The dNerva lung denervation COPD responder profile (RV≥175% pred. and Emphysema ≤20%) will be prospectively evaluated in AIRFLOW-4 (NCT07051707).

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