

Safety and Adverse Events after Targeted Lung Denervation for Symptomatic Moderate to Severe Chronic Obstructive Pulmonary Disease (AIRFLOW)

A Multicenter Randomized Controlled Clinical Trial

Dirk-Jan Slebos^{1*}, Pallav L. Shah^{2*}, Felix J. F. Herth^{3,4}, Christophe Pison⁵, Christian Schumann⁶, Ralf-Harto Hübner⁷, Peter I. Bonta⁸, Romain Kessler⁹, Wolfgang Gesierich¹⁰, Kaid Darwiche¹¹, Bernd Lamprecht¹², Thierry Perez¹³, Dirk Skowasch¹⁴, Gaetan Deslee¹⁵, Armelle Marceau¹⁶, Frank C. Scirba¹⁷, Reinoud Gosens¹⁸, Jorine E. Hartman¹, Karthi Srikanthan², Marina Duller¹⁹, and Arschang Valipour¹⁹; on behalf of the AIRFLOW-2 Study Group

¹Department of Pulmonary Diseases and ¹⁸Department of Molecular Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; ²Royal Brompton & Harefield NHS Trust, Chelsea & Westminster Hospital and Imperial College London, London, United Kingdom; ³Department of Pneumology and Critical Care Medicine, Thoraxklinik, and ⁴Translational Lung Research Center Heidelberg, University of Heidelberg, Heidelberg, Germany; ⁵CHU Grenoble Alpes, Service Universitaire Pneumologie Physiologie, Université Grenoble Alpes, Grenoble, France; ⁶Clinic of Pneumology, Thoracic Oncology, Sleep and Respiratory Critical Care, Klinikverbund Kempten-Oberallgäu, Kempten and Immenstadt, Germany; ⁷Charité Universitätsmedizin Berlin, Medizinische Klinik m. Schw. Infektiologie und Pneumologie, Campus Virchow, Berlin, Germany; ⁸Department of Respiratory Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; ⁹Service de Pneumologie, Nouvel Hôpital Civil, Université de Strasbourg, Strasbourg, France; ¹⁰Asklepios-Fachkliniken Munich-Gauting, Comprehensive Pneumology Center Munich, Gauting, Germany; ¹¹Department of Pulmonary Medicine, Section of Interventional Pneumology, Ruhlandklinik–University Hospital Essen, University of Duisburg-Essen, Essen, Germany; ¹²Department of Pulmonary Medicine, Kepler Universitätsklinikum GmbH, Linz, Austria; ¹³CHU de Lille–Hôpital Calmette, Lille, France; ¹⁴Department of Internal Medicine II–Cardiology/Pneumology, University of Bonn, Bonn, Germany; ¹⁵CHU de Reims, Hôpital Maison Blanche, Service de Pneumologie, Reims, France; ¹⁶Service de Pneumologie, Hôpital Universitaire Bichat, Paris, France; ¹⁷University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; and ¹⁹Department of Respiratory and Critical Care Medicine, Karl-Landsteiner-Institute for Lung Research and Pulmonary Oncology, Krankenhaus Nord–Klinik Floridsdorf, Vienna, Austria

ORCID IDs: 0000-0002-9052-4638 (P.L.S.); 0000-0003-0681-1325 (K.D.).

Abstract

Rationale: Targeted lung denervation (TLD) is a bronchoscopic radiofrequency ablation therapy for chronic obstructive pulmonary disease (COPD), which durably disrupts parasympathetic pulmonary nerves to decrease airway resistance and mucus hypersecretion.

Objectives: To determine the safety and impact of TLD on respiratory adverse events.

Methods: We conducted a multicenter, randomized, sham bronchoscopy–controlled, double-blind trial in patients with symptomatic (modified Medical Research Council dyspnea scale score, ≥ 2 ; or COPD Assessment Test score, ≥ 10) COPD (FEV₁, 30–60% predicted). The primary endpoint was the rate of respiratory adverse events between 3 and 6.5 months after randomization (defined as COPD exacerbation, tachypnea, wheezing, worsening bronchitis, worsening dyspnea, influenza, pneumonia, other respiratory infections, respiratory failure, or airway effects requiring therapeutic intervention). Blinding was maintained through 12.5 months.

Measurements and Main Results: Eighty-two patients (50% female; mean \pm SD: age, 63.7 \pm 6.8 yr; FEV₁, 41.6 \pm 7.3% predicted; modified Medical Research Council dyspnea scale score, 2.2 \pm 0.7;

COPD Assessment Test score, 18.4 \pm 6.1) were randomized 1:1. During the predefined 3- to 6.5-month window, patients in the TLD group experienced significantly fewer respiratory adverse events than those in the sham group (32% vs. 71%, $P = 0.008$; odds ratio, 0.19; 95% confidence interval, 0.0750–0.4923, $P = 0.0006$). Between 0 and 12.5 months, these findings were not different (83% vs. 90%; $P = 0.52$). The risk of COPD exacerbation requiring hospitalization in the 0- to 12.5-month window was significantly lower in the TLD group than in the sham group (hazard ratio, 0.35; 95% confidence interval, 0.13–0.99; $P = 0.039$). There was no statistical difference in the time to first moderate or severe COPD exacerbation, patient-reported symptoms, or other physiologic measures over the 12.5 months of follow-up.

Conclusions: Patients with symptomatic COPD treated with TLD combined with optimal pharmacotherapy had fewer study-defined respiratory adverse events, including hospitalizations for COPD exacerbation.

Clinical trial registered with www.clinicaltrials.gov (NCT02058459).

Keywords: chronic obstructive pulmonary disease; nerves; targeted lung denervation; anticholinergic; bronchoscopy

(Received in original form March 14, 2019; accepted in final form August 12, 2019)

©This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

*These authors contributed equally to this work.

Am J Respir Crit Care Med Vol 200, Iss 12, pp 1477–1486, Dec 15, 2019

Copyright © 2019 by the American Thoracic Society

Originally Published in Press as DOI: 10.1164/rccm.201903-0624OC on August 12, 2019

Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the

Subject: Targeted lung denervation is a novel bronchoscopic therapy that disrupts parasympathetic pulmonary nerve input to the lung to reduce the clinical consequences of cholinergic hyperactivity.

What This Study Adds to the Field:

Results of the AIRFLOW-2 study build on the growing evidence in the literature that targeted lung denervation is an acceptably safe procedure and has the potential to reduce respiratory system–related adverse events and chronic obstructive pulmonary disease exacerbations that require hospitalization.

A large subset of patients with chronic obstructive pulmonary disease (COPD) remain symptomatic and continue to experience frequent exacerbations despite optimal medical treatment (1–5). In COPD, acetylcholine released from parasympathetic airway nerve fibers mediates smooth muscle tone, reflex bronchoconstriction, mucus hypersecretion, and airway inflammation, which all contribute to disease symptoms and progression (6–10). Targeting the parasympathetic nerve system in COPD with anticholinergic inhaler therapy has the potential to reduce COPD exacerbations (11, 12). A more permanent disruption of neuronal acetylcholine release would therefore be a therapeutic complement to muscarinic receptor blockade in the lung (13). The roles of vagal afferent and parasympathetic efferent innervation of the lung during reflex bronchoconstriction and inflammation/viral infection–induced airway hyperresponsiveness have been reviewed extensively (8, 14), and they

provide a rationale for the potential impact of lung denervation on exacerbations in obstructive airway disease. A novel bronchoscopic procedure called “targeted lung denervation” (TLD) has been developed for COPD, with the intention of disruption of the peribronchial vagal innervation of the lungs (13). Previous studies of TLD in COPD have demonstrated proof of concept, optimal dosing, an extended safety profile, and potential efficacy outcomes (15–17). The current AIRFLOW-2 trial prospectively evaluated the safety of this intervention, with the effect on respiratory adverse events as the primary outcome, in patients with symptomatic moderate to severe COPD. Some of the results of these studies have been reported previously in the form of an abstract (18).

Methods

Study Design and Oversight

This study is a randomized, sham-controlled, double-blind, prospective, multicenter study designed to evaluate the safety of TLD in patients with moderate to severe COPD (AIRFLOW-2 trial). Patients were randomly assigned 1:1 to a sham procedure or TLD and followed for 12.5 months for the primary and secondary endpoints, after which they were unblinded. All local ethics committees of the participating hospitals approved the study, and all patients provided written informed consent.

The double-blinding was achieved by two separated study teams: an unblinded treatment team not involved in any of the follow-up and a separate blinded assessment team that performed all follow-up assessments and was not involved in or present for the procedure. On the procedure day, patients were randomized after administration of anesthesia.

Randomization schemes (permuted blocks of 4 and 2) were generated by the independent statistical group NAMSA in sequentially labeled, sealed, and tamper-resistant randomization envelopes (*see* online supplement). Study principal investigators and the sponsor designed the protocol. NAMSA independently validated the study results. An independent data and safety monitoring board was responsible for overall safety, and a clinical events committee adjudicated all serious adverse events and any event requested by the medical safety officer (*see* online supplement).

Study Patients

Patients aged between 40 and 75 years, with a diagnosis of moderate to severe symptomatic COPD (post-bronchodilator FEV₁/FVC ratio <0.70 and FEV₁ 30–60% of predicted), and with a modified Medical Research Council dyspnea scale (mMRC) score greater than or equal to 2 or a COPD Assessment Test score greater than or equal to 10 were enrolled (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage B or D patients). Major exclusion criteria were more than two respiratory system–related hospitalizations within the past year, Gastroparesis Cardinal Symptom Index greater than or equal to 18 (19), and previous lung or chest procedure (Table E1 in the online supplement).

Drug Requirements during the Study

Patient inhaler use was documented at screening. During washout, long-acting muscarinic antagonists (LAMAs) were held for 7 days, ultra-long-acting β -agonists were held for 72 hours, long-acting β -agonists (LABAs) were held for 24 hours, and short-acting β -agonists and short-acting muscarinic antagonists (SAMAs) were held for 12 hours. After washout, all patients were placed on inhaled tiotropium 18 μ g/d and could continue

A complete list of AIRFLOW-2 Study Group members may be found before the beginning of the REFERENCES.

Supported by Nuaira, Inc., Minneapolis, Minnesota.

Author Contributions: Had full access to all the data in the study, take responsibility for the integrity of the data and the accuracy of the data analysis, and had authority over manuscript preparations and the decision to submit the manuscript for publication: D.-J.S., P.L.S., and A.V. Study concept and design: D.-J.S., P.L.S., and A.V. Acquisition, analysis, and interpretation of data: all authors. Drafting of the manuscript: D.-J.S., P.L.S., and A.V. Critical revision of the manuscript for important intellectual content: all authors. Study supervision, patient recruitment, and follow-up: all authors.

Correspondence and requests for reprints should be addressed to Arschang Valipour, M.D., Karl-Landsteiner-Institute for Lung Research and Pulmonary Oncology, Krankenhaus Nord-Klinik Floridsdorf, Brünner Straße 68, 1210 Wien, Vienna, Austria. E-mail: arschang.valipour@wienkav.at.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

other inhalers, such as LABAs, short-acting muscarinic antagonists, short-acting β -agonists, and inhaled corticosteroids (ICS), at the discretion of their physician. Patients were required to continue LAMAs and other maintenance medications through the 6-month follow-up visit and were encouraged to continue through the 12-month visit.

Study Procedures

Patients underwent baseline testing after a 7-day washout period. Baseline and follow-up testing included spirometry, body plethysmography (both performed according to American Thoracic Society [ATS]/European Respiratory Society guidelines [20]), constant work rate cycle ergometry (performed according to ATS/American College of Chest Physicians guidelines [21]), and health-related quality of life questionnaires: COPD-specific St. George's Respiratory Questionnaire (SGRQ-C; scores range from 0 to 100, with lower scores indicating better health-related quality of life; minimal clinically important difference [MCID], 4 points) (22, 23), EuroQoL 5-dimensions (EQ-5D-5L) (scores range from 0 to 1; MCID, 0.05 points), EuroQoL visual analogue scale (EQ-5D VAS; scores range from 0 to 100; MCID, 7–10 points) (24), COPD Assessment Test (25) (scores range from 0 to 40, with lower scores indicating less symptoms; MCID, 2 points), mMRC (26) (scores range from 0 to 4, with lower scores indicating less dyspnea; MCID, 1 point), Baseline Dyspnea Index and Transitional Dyspnea Index (27) (scores range from –9 to 9, with lower scores indicating a lesser change in dyspnea; MCID, 1 point), and the Patient Assessment of Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM) (28) (total score range 0–100, with higher scores representing more gastrointestinal symptoms). A baseline computed tomographic (CT) scan of the chest was required to confirm appropriate bronchial anatomy, calculate emphysema scores, and rule out other pulmonary abnormalities.

Washout baseline testing was followed by a minimum 7-day run-in period while receiving tiotropium and included lung function and questionnaires performed 24 hours after the last dose of tiotropium to establish

trough baseline values. Details of respiratory medication use during baseline and follow-up pulmonary function testing can be found in the study protocol (Appendix E6, AIRFLOW-2 Protocol, subsection 7.8.2, Table E3). All patients underwent early safety evaluation by phone at 7 days and by hospital visits at 30 and 90 days after the procedure. On-drug testing was repeated at 6 and 12 months, and washout testing was repeated at 6.5 and 12.5 months. All adverse events were reported and tracked throughout the entire study period.

Study Procedure

The bronchoscopy was performed with the patients under general anesthesia. Patients allocated to the treatment arm received Nuvaira lung denervation therapy (Nuvaira, Inc.) (Appendix E2, Figure E1). In summary, a low-pressure contrast balloon was inflated in the esophagus to visualize and assess the distance of the esophagus from the TLD catheter during treatment in order to avoid the esophageal nerve plexus during radiofrequency (RF) ablation. After advancement of the TLD catheter, visual assessment and fluoroscopy were performed to confirm electrode position. The catheter

Table 1. Baseline Characteristics and Medication of the Patients at Screening

	Sham Group (n = 41)	TLD Group (n = 41)
Characteristic		
Age, yr	63.68 ± 7.0	63.71 ± 6.7
Male sex, n (%)	19 (46.3)	22 (53.7)
White race, n (%)	40 (97.6)	40 (97.6)
BMI, kg/m ²	25.66 ± 4.2	25.44 ± 3.8
Smoking, pack-years	48.63 ± 30.7	43.49 ± 22.6
At least one respiratory hospitalization in 12 mo before randomization, n (%)	10 (24)	10 (24)
Emphysema score*, %	25.34 ± 10.7	27.92 ± 12.9
Total SGRQ-C score* [†]	51.72 ± 15.5	54.88 ± 17.7
CAT	18.9 ± 6.6	17.9 ± 6.7
mMRC	2.1 ± 0.6	2.3 ± 0.8
BDI	5.9 ± 1.8	5.1 ± 2.1
PAGI-SYM	0.37 ± 0.5	0.37 ± 0.4
Post-bronchodilator FEV ₁ , L	1.14 ± 0.32	1.18 ± 0.39
Post-bronchodilator FEV ₁ , % predicted	41.4 ± 7.2	41.9 ± 7.6
Post-bronchodilator FVC, L	3.07 ± 1.05	3.11 ± 0.88
Post-bronchodilator FVC, % predicted	89.4 ± 18.9	90.8 ± 16.2
Post-bronchodilator FEV ₁ /FVC	0.39 ± 0.09	0.38 ± 0.08
Medication		
Optimal bronchodilator therapy (LAMA, LAMA/LABA, or LAMA/LABA/ICS), % (n)	93% (38/41)	95% (39/41)
Single therapy		
LAMA use, % (n)	2% (1/41)	0% (0/41)
ICS use, % (n)	2% (1/41)	0% (0/41)
Double therapy		
LABA/LAMA, % (n)	24% (10/41)	39% (16/41)
LABA/ICS, % (n)	2% (1/41)	5% (2/41)
Triple therapy		
LABA/LAMA/ICS, % (n)	68% (28/41)	56% (23/41)

Definition of abbreviations: BDI = Baseline Dyspnea Index; BMI = body mass index; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting β -agonist; LAMA = long-acting muscarinic antagonist; mMRC = modified Medical Research Council dyspnea scale; PAGI-SYM = Patient Assessment of Gastrointestinal Disorders Symptom Severity Index; SGRQ-C = St. George's Respiratory Questionnaire for COPD; TLD = targeted lung denervation.

No significant difference between sham and TLD groups were found, $P > 0.05$. Assessments were performed at screening visit on standard drug therapy. Plus-or-minus values are mean \pm SD. There were no significant differences between groups.

*Scores on the SGRQ-C range from 0 to 100, with a lower score indicating better health status.

[†]Emphysema score is presented as the percentage of voxels with attenuation below –950 Hounsfield units.

was rotated to achieve a circumferential band of ablation along the external wall of the main airways. For the sham group, blinding was ensured by performing an entire mock procedure with a taped recording of the functional console procedure sounds. Treatments under this protocol were scheduled as outpatient procedures unless an overnight stay was required per hospital protocol. All patients were prescribed standard doses of steroids and antibiotics on the day of and for 2 days after the study procedure as prophylaxis related to standard interventional bronchoscopy.

Endpoints

The primary endpoint was the difference between the treatment and sham groups in the rate (percentage) of respiratory adverse events between 3 and 6.5 months after treatment. The time window for the primary endpoint was set to evaluate the effect of TLD on respiratory safety in isolation from the effects of bronchoscopy. On the basis of previous pulmonary device trials, it was assumed that the effect of the bronchoscopy on respiratory system-related events in both arms would have resolved and any lingering differences in the percentage of patients experiencing an event would be due to the treatment. Respiratory adverse events were predefined as respiratory failure, COPD exacerbation, influenza, pneumonia, respiratory infection, worsening bronchitis, worsening dyspnea, tachypnea, wheezing, or local airway effects that required a therapeutic intervention. Primary performance endpoints included 1) device success, defined as the ability to insert, place, and remove the device; and 2) technical success, defined as the ability to deliver RF energy to each intended location.

Per protocol, the respiratory adverse events defined as the primary endpoint were tracked for the entire study period from 0 to 12.5 months. Secondary safety measures included overall rates and severity of adverse events and acute procedure success. Acute procedure success was defined as device success without the occurrence of an in-hospital serious adverse event before discharge. Quality-of-life measures, dyspnea score, lung function measures, and exercise tolerance were evaluated as exploratory secondary endpoints.

Rate of all Respiratory Events from 3 to 6.5 months

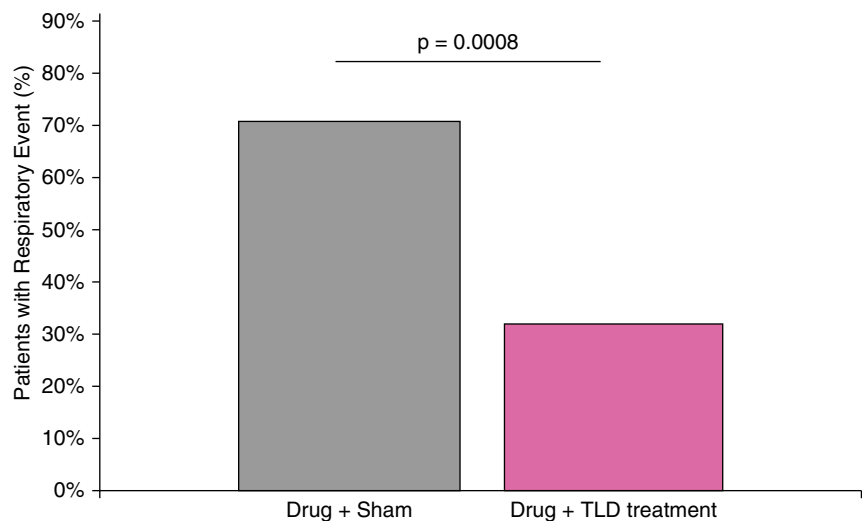


Figure 1. Respiratory adverse events between 3 and 6.5 months after bronchoscopy for the sham bronchoscopy and targeted lung denervation (TLD) groups. Respiratory events were lower respiratory tract complaints as defined by the investigator, including respiratory failure, pneumonia, chronic obstructive pulmonary disease exacerbation, influenza, respiratory infection, worsening bronchitis, worsening dyspnea, tachypnea, wheezing, or discovered airway effects that require a therapeutic intervention.

Statistical Methods

Statistical hypothesis tests are based on *t* tests for continuous data that are normally distributed. Nonparametric tests were performed when there was

evidence of nonnormality. Fisher's exact test was used to compare categorical data or when data were expressed as a percentage. Comparisons between groups of time-to-event data, such as

Table 2. Total Predefined Primary Endpoint Respiratory Adverse Events 3–6.5 Months after Procedure

Diagnosis (Patient Could Have Multiple Events)	Sham Group (n = 41) [% (n)]	TLD Group (n = 41) [% (n)]	P Value
Bronchitis, worsening	4.9 (2)	—	0.4938
COPD exacerbation	43.9 (18)	26.8 (11)	0.1731
Discovered airway effects that require a therapeutic intervention	—	2.4 (1)*	1.0000
Dyspnea, worsening	22.0 (9)	4.9 (2)	0.0496
Influenza	2.4 (1)	—	1.0000
Pneumonia	4.9 (2)	2.4 (1)	1.0000
Respiratory infection	—	—	—
Respiratory failure	—	—	—
Tachypnea	—	—	—
Wheezing	2.4 (1)	—	1.0000
Total	70.7 (29)	31.7 (13)	0.0008

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; TLD = targeted lung denervation.

The numbers are displayed as the percentage of patients with at least one event (total number of patients with at least one event). The statistical comparison was performed with the percentage of patients using Fisher's exact test. The total also contains patients with multiple different event diagnoses. Respiratory adverse events were predefined as respiratory failure, COPD exacerbation, influenza, pneumonia, respiratory infection, worsening bronchitis, worsening dyspnea, tachypnea, wheezing, or local airway effects that required a therapeutic intervention.

*See appendix in the online supplement for event description.

time to first COPD exacerbation, were accomplished using a standard log-rank statistic. Though the sample size was not determined on the basis of *a priori* power considerations for hypothesis testing, *P* values are provided for exploratory endpoints to help further quantify and frame the results.

The focus of this study was safety, particularly in the TLD group, in which 41 subjects were randomized. To that end, adverse events with a nominal incidence rate of 7% have a probability of 95% of being detected during the course of this trial within the TLD group. Importantly, the primary endpoint—respiratory system-related adverse events between 3 and 6.5 months—had an incidence rate greater than 7% and therefore should be representative and allow characterization of the effect of TLD.

Results

Patient Characterization and Procedural Aspects

The study inclusion was conducted between July 2016 and May 2017. One hundred ninety-four patients were screened, and 82 patients were randomized (*see* Table 1 for baseline demographics; *see also* Consolidated Standards of Reporting Trials flowchart in Figure E2). Three patients in the treatment arm and four patients in the sham arm exited early. The median procedure times were 40 minutes for the sham group (range, 27–63 min) and 74 minutes for the TLD procedure (range, 43–133 min). The median length of hospital stay was 1 day (range, 0–4 d) for both groups.

Primary Outcomes

Primary safety endpoint. The rate of predefined respiratory adverse events between 3 and 6.5 months after the procedure was 71% (29 of 41) in the sham arm and 32% (13 of 41) in the TLD arm ($P=0.0008$). The most common events in both groups were COPD exacerbation and dyspnea (Figure 1 and Tables 2 and 3). There were no differences in the rate of respiratory system-related adverse events between patients in the treatment and control arms during the initial 3-month post-procedure period or over the entire 0- to 12.5-month study period (Table 4).

Primary performance outcomes. Device success, defined as the ability to insert, place, and remove the device, was 100%. Technical success (the ability to deliver RF energy to each intended location) was 90% (38 of 42 patients). Full circumferential treatment (four activations) could not be completed in 16% of left main bronchi and 46% of right main bronchi, principally due to anatomical proximity to the esophagus. On average, 83% of the right mainstem and 94% of the left mainstem was treated.

Secondary Outcomes

Secondary respiratory safety measures. The risk of severe COPD exacerbation requiring hospitalization was significantly lower in the TLD treatment group than in the sham patient group at 12.5 months after randomization, as assessed in a time-to-first-event analysis (hazard ratio, 0.35; 95% confidence interval, 0.13–0.99; $P=0.0390$) (Figure 2A). In the 1 year of follow-up AIRFLOW-2, 32% (13 of 41 sham) and

12% (5 of 41 TLD) of patients experienced a hospitalization for COPD exacerbation. In each arm, 10 (24%) of 41 patients had a prior-year hospitalization for a COPD exacerbation. In the sham arm, 7 (70%) of the 10 were readmitted for COPD exacerbation in the study period, whereas only 2 (20%) of the 10 were readmitted in the TLD arm ($P=0.0698$). Of 31 patients in the TLD arm without a prior-year hospitalization, 9.7% (3 of 31) were hospitalized for COPD exacerbation during the trial, as compared with 19.4% (6 of 31) in the sham arm ($P=0.473$). There was no statistical difference in risk of first moderate or severe COPD exacerbation, defined as exacerbations requiring treatment with systemic steroids and/or antibiotics, with or without hospitalization, over the 0- to 12.5-month study in the treatment arm compared with the control group (hazard ratio, 0.66; 95% confidence interval, 0.38–1.16; $P=0.1498$) (Figure 2B). *See* Appendix E4 for reporting of all adverse events.

Table 3. Nonserious Respiratory Adverse Events 3–6.5 Months after Procedure

Diagnosis (Patient Could Have Multiple Events)	Sham Group (n = 41) [% (n)]	TLD Group (n = 41) [% (n)]	P Value
Bronchitis, worsening	4.9 (2)	—	0.4938
Common cold*	4.9 (2)	4.9 (2)	1.0000
Congestion	—	—	—
COPD exacerbation†	36.6 (15)	17.1 (7)	0.0797
Cough	14.6 (6)	2.4 (1)	0.1088
Dyspnea, worsening	17.1 (7)	4.9 (2)	0.1549
Hemoptysis	—	—	—
Hoarseness‡	4.9 (2)	2.4 (1)	1.0000
Increased mucus§	2.4 (1)	2.4 (1)	1.0000
Influenza	2.4 (1)	—	1.0000
Mucosal candidiasis	—	—	—
Pneumonia	2.4 (1)	—	1.0000
Pulmonary infection	—	—	—
Rhinitis/pollinosis	—	—	—
Sore throat¶	—	2.4 (1)	1.0000
Thoracic pain	—	—	—
Wheezing	2.4 (1)	—	1.0000
Total	65.9 (27)	34.1 (14)	0.0077

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; TLD = targeted lung denervation.

The table includes nonserious adverse events with reported start dates 80–205 days after procedure belonging to the respiratory, thoracic, and mediastinal disorders SOC (System Organ Class in MedDRA version 20.0) as of June 15, 2018. The numbers are displayed as the percentage of patients with at least one event (total number of patients with at least one event). The statistical comparison was performed with the percentage of patients using Fisher's exact test.

*Includes the following MedDRA preferred terms: viral upper respiratory tract infection, upper respiratory tract infection, and respiratory tract infection.

†MedDRA preferred term is chronic obstructive pulmonary disease.

‡Includes the following MedDRA preferred terms: dysphonia and throat irritation.

§MedDRA preferred term is productive cough.

¶MedDRA preferred term is tonsillitis.

Table 4. Total Predefined Respiratory Adverse Events 0–3 and 0–12.5 Months after Procedure

Diagnosis	Sham Group (n = 41) [% (n)]	TLD Group (n = 41) [% (n)]	P Value
Bronchitis, worsening			
0–3 mo	4.9 (2)	2.4 (1)	1.0
0–12.5 mo	9.8 (4)	9.8 (4)	1
COPD exacerbation			
0–3 mo	22.0 (9)	22.0 (9)	1.0
0–12.5 mo	68.3 (28)	53.7 (22)	0.5641
Discovered airway effects that require a therapeutic intervention			
0–3 mo	—	—	—
0–12.5 mo	—	2.4 (1)*	1.0000
Dyspnea, worsening			
0–3 mo	9.8 (4)	12.2 (5)	1.0
0–12.5 mo	36.6 (15)	22.0 (9)	0.3526
Influenza			
0–3 mo	—	4.9 (2)	0.4938
0–12.5 mo	2.4 (1)	9.8 (4)	0.3597
Pneumonia			
0–3 mo	4.9 (2)	4.9 (2)	1.0
0–12.5 mo	17.1 (7)	12.2 (5)	0.7578
Respiratory infection			
0–3 mo	—	—	—
0–12.5 mo	—	—	—
Respiratory failure			
0–3 mo	—	—	—
0–12.5 mo	—	—	—
Tachypnea			
0–3 mo	—	—	—
0–12.5 mo	—	—	—
Wheezing			
0–3 mo	—	4.9 (2)	0.4942
0–12.5 mo	2.4 (1)	4.9 (2)	1
Total			
0–3 mo	36.6 (15)	46.3 (19)	0.3766
0–12.5 mo	90.2 (37)	82.9 (34)	0.5187

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; TLD = targeted lung denervation.

The numbers are displayed as the percentage of patients with at least one event (total number of patients with at least one event in parentheses). The statistical comparison was performed with the percentage of patients using Fisher's exact test. The total also contains patients with multiple different event diagnoses. Respiratory adverse events were predefined as respiratory failure, COPD exacerbation, influenza, pneumonia, respiratory infection, worsening bronchitis, worsening dyspnea, tachypnea, wheezing, or local airway effects that required a therapeutic intervention.

*See appendix in the online supplement for event description.

Secondary efficacy measures. No significant between-group differences at 12 months were found in symptom or physiologic measures (Table 5).

Secondary overall safety. The overall number of serious adverse events was similar between groups, except for differences in respiratory adverse events (described above; see also Appendix E4 and Table E2). Although there was no statistical difference in gastrointestinal adverse events, there was a trend for increased gastrointestinal events in the TLD

arm (Appendix E4 and Table E2). There were five patients with gastrointestinal serious adverse events (see Appendix E5 for detailed description of events). At 1 month, there was a transient increase in the PAGI-SYM score for the treatment group compared with the sham group (0.44 vs. -0.21 ; $P=0.009$). However, no significant differences in changes of the PAGI-SYM score between the treatment and sham groups were observed further out: 0.17 vs. -0.04 ($P=0.1991$) at 3 months; 0.14 vs. -0.03 ($P=0.1796$) at 6 months; -0.16 vs.

-0.26 ($P=0.4058$) at 9 months; and 0.12 vs. -0.06 ($P=0.1757$) at 12 months. Chest CT scans from the 1-year follow-up were analyzed, and they demonstrated no treatment-related abnormalities.

Discussion

We performed a randomized, double-blind, full sham bronchoscopy-controlled study of TLD in patients with symptomatic COPD. We demonstrated that TLD on top of maintenance inhaler therapy is a safe and feasible treatment. TLD was associated with fewer respiratory adverse events in the primary endpoint time window and hospitalization for COPD exacerbations over the 1 year of follow-up compared with control patients who underwent a sham procedure and remained blinded to their treatment allocation for 1 year.

Targeting the airway parasympathetic system with anticholinergic monotherapy was previously reported to reduce exacerbations in the UPLIFT (Understanding Potential Long-Term Impacts on Function with Tiotropium) and GLOW2 (1-year Study to Assess the Efficacy, Safety, and Tolerability of Glycopyrronium Bromide [NVA237] in Chronic Obstructive Pulmonary Disease [COPD]) studies (29, 30) and was demonstrated to be as effective as LABA/ICS therapy in the INSPIRE (SERETIDE 50/500 mcg versus Tiotropium Bromide on Exacerbation Rates in Severe Chronic Obstructive Pulmonary Disease) study (31). Although we acknowledge that the present study was not able to answer the question of how TLD specifically impacts severe exacerbation rates in COPD, the true pathophysiological effects of anticholinergic inhaler therapy on exacerbation outcomes similarly remain speculative. Currently postulated mechanisms responsible for targeting the airway parasympathetic system, either with LAMA or with TLD, may involve multiple pathways, such as reductions in symptom variability, airway hyperresponsiveness, mucus production, impaired mucociliary clearance, and/or hyperinflation (6–10, 32, 33).

Furthermore, Zanini and colleagues demonstrated that airway hyperresponsiveness was associated with the number and severity of exacerbations and symptoms in COPD (34). Whole-lung airway hyperresponsiveness is mediated by vagal reflex pathways (8, 35). It has been

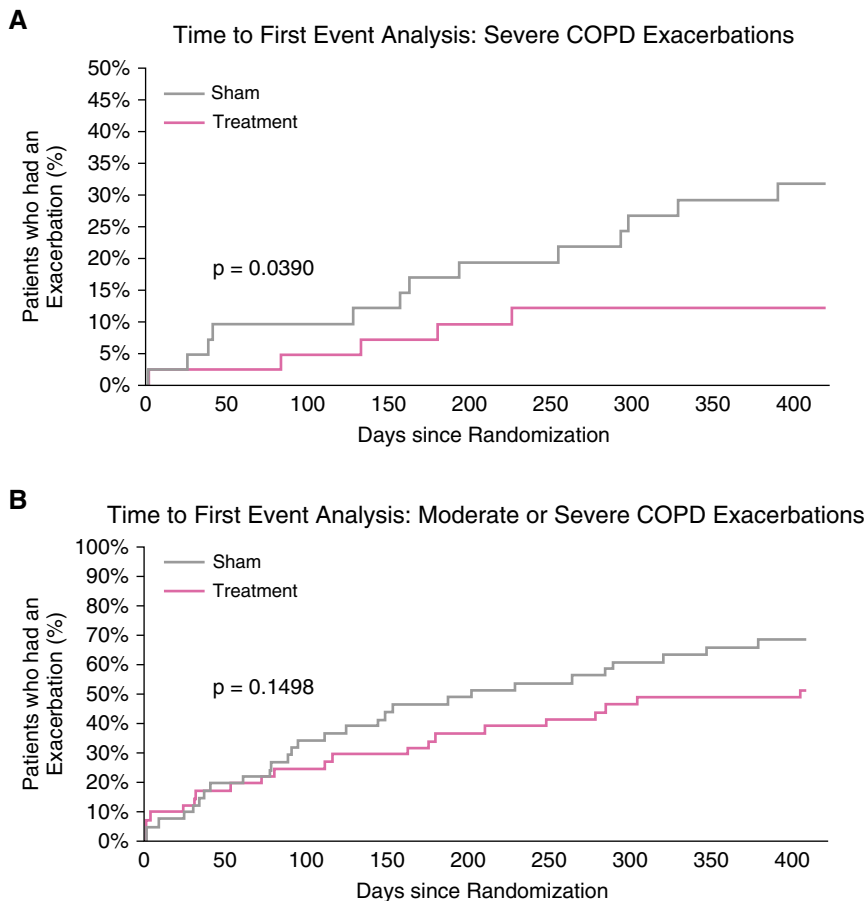


Figure 2. (A) Time-to-first-event analysis: severe chronic obstructive pulmonary disease (COPD) exacerbations. (B) Time-to-first-event analysis: moderate or severe COPD exacerbations.

shown that an intact vagus nerve is required for hyperresponsiveness in animal models of airway inflammation (36, 37). In humans with viral infections, muscarinic blockade with atropine attenuates bronchial hyperresponsiveness to histamine (38). TLD disrupts these reflex pathways, and thus the therapy may impact severe exacerbation rates by attenuating bronchial hyperresponsiveness and basal nerve tone (13).

Given that the present study did not require an exacerbation history for inclusion, a relatively high rate of COPD exacerbations was observed in the 1 year of follow-up in this study. In terms of severe COPD exacerbations, 32% (sham) and 12% (TLD) of patients experienced a hospitalization for COPD exacerbation during 1 year of follow-up in AIRFLOW-2 (24% of patients in each arm had a hospitalization in the prior year). A similarly high rate of hospitalized exacerbations in the sham arm of the METREX (Study to Evaluate

Efficacy and Safety of Mepolizumab for Frequently Exacerbating Chronic Obstructive Pulmonary Disease [COPD] Patients) study was also observed (4). On the basis of baseline patient characteristics, the METREX study enrolled patients with a similar disease profile and rate of respiratory system–related hospitalizations in the prior year, as in the present study.

It seems unlikely that medication changes could have influenced exacerbation rates, with 95% of patients entering this study on triple or dual therapy and with 91% maintaining their baseline regimens through 1 year of follow-up. Furthermore, the observed change in severe COPD exacerbation frequency between the year before treatment and the year after suggests an intriguing *post hoc* signal that may represent a treatment effect of TLD independent of other confounders. Confirmation of these observations will require a larger, higher-powered study.

Apart from an improvement in the dyspnea score (Transitional Dyspnea Index)

at 6 months, there were no significant differences in secondary efficacy measures. However, it is difficult to interpret these results, given that the study was not powered to detect differences between the secondary outcomes. In terms of changes in lung function, TLD has been compared with baseline LAMA therapy in previous single-arm registries (15–17, 39). These previous trials showed changes in FEV₁ after TLD that are similar to those of tiotropium alone (trough effect). The present study is the first to evaluate TLD in a population of patients who were largely receiving dual bronchodilator therapy. When given alone and compared with a placebo, tiotropium (a LAMA) (30, 40) and salmeterol (a LABA) (41) have been shown to provide between 100 and 150 ml of improvement in trough (prebronchodilator) lung function. When the LABAs and LAMAs are combined, the trough bronchodilator effect is not additive, showing at most 80 ml of additional benefit (42). The effect of an additional bronchodilator therapy on top of two existing bronchodilators has not been studied. The addition of ICS, which is not intended as a bronchodilator, on top of LABA/LAMA therapy was shown to produce a 54-ml change in trough FEV₁ in one study (3). Greater than 50% of patients in the AIRFLOW-2 study were receiving LABA/LAMA/ICS therapy. There were no significant differences in change in pulmonary function from baseline between the TLD and sham groups.

A growing body of literature examining the effect of therapeutics on reductions in COPD exacerbations demonstrates only modest changes in secondary outcomes in association with clinically meaningful reduction of exacerbations. In the SPARK (Effect of QVA149 versus NVA237 and Tiotropium on Chronic Obstructive Pulmonary Disorder [COPD] Exacerbations) trial comparing dual and single therapy, reduction of moderate or severe exacerbations by 11% was associated with an SGRQ-C change that ranged from –1.7 to –3.1 and an FEV₁ change between 60 and 80 ml (43). The recent IMPACT (A Study Comparing the Efficacy, Safety and Tolerability of Fixed Dose Combination [FDC] of FF/UMEC/VI with the FDC of FF/VI and UMEC/VI; Administered Once Daily via a Dry Powder Inhaler [DPI] in Subjects with Chronic Obstructive Pulmonary Disease [COPD]) trial comparing triple therapy with dual

Table 5. Secondary Outcomes

Outcome	Sham Group (On Drug, Compared with Baseline Off Drug) (n = 41) [Mean ± SD (n)]	TLD Group (On Drug, Compared with Baseline Off Drug) (n = 41) [Mean ± SD (n)]	P Value for Sham vs. TLD (t Test)
FEV ₁ , ml			
6 mo	86.41 ± 179.5 (39)	127.6 ± 201.0 (38)	0.3453
12 mo	103.5 ± 192.7 (37)	74.32 ± 213.1 (37)	0.5386
FVC, ml			
6 mo	147.2 ± 360.8 (39)	240.0 ± 389.7 (38)	0.2815
12 mo	211.4 ± 411.8 (37)	235.4 ± 471.1 (37)	0.8158
RV, L			
6 mo	-0.09 ± 0.9 (38)	-0.32 ± 0.8 (38)	0.2431
12 mo	-0.23 ± 0.8 (37)	-0.35 ± 0.6 (37)	0.4770
SGRQ-C			
6 mo	-3.76 ± 13.8 (39)	-8.31 ± 12.6 (37)	0.1382
12 mo	-2.46 ± 14.5 (38)	-5.05 ± 14.4 (37)	0.4414
TDI			
6 mo	-1.51 ± 3.7 (39)	0.25 ± 3.2 (36)	0.0318
12 mo	-1.24 ± 3.4 (38)	-1.17 ± 3.1 (36)	0.9268
CAT			
6 mo	-3.18 ± 8.0 (39)	-1.97 ± 6.5 (38)	0.4720
12 mo	-3.24 ± 8.3 (38)	-0.89 ± 6.4 (37)	0.1754
mMRC			
6 mo	-0.26 ± 1.0 (39)	-0.47 ± 1.0 (38)	0.3368
12 mo	-0.21 ± 1.0 (38)	-0.44 ± 0.8 (36)	0.2790
EQ-5D			
6 mo	0.03 ± 0.2 (38)	0.06 ± 0.1 (37)	0.2868
12 mo	-0.01 ± 0.2 (38)	0.02 ± 0.2 (37)	0.4374
EQ-5D VAS			
6 mo	3.11 ± 21.5 (38)	9.11 ± 22.5 (37)	0.2415
12 mo	6.03 ± 23.1 (38)	6.68 ± 20.9 (37)	0.8988
PAGI-SYM score			
6 mo	-0.03 ± 0.5 (39)	0.14 ± 0.6 (37)	0.1796
12 mo	-0.06 ± 0.5 (38)	0.12 ± 0.7 (36)	0.1757
CWRE*, min			
6 mo	1.24 ± 4.49 (35)	1.25 ± 6.31 (37)	0.9935
12 mo	0.77 ± 7.6 (34)	0.85 ± 7.4 (35)	0.9649

Definition of abbreviations: CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; CWRE = constant work rate cycle ergometry; EQ-5D = EuroQol Global Health Assessment–5 dimensions; EQ-5D VAS = EQ-5D visual analogue scale, score range 0–100; mMRC = modified Medical Research Council dyspnea scale; PAGI-SYM = Patient Assessment of Gastrointestinal Disorders Symptom Severity Index; RV = residual volume; SGRQ-C = St. George's Respiratory Questionnaire for COPD; TDI = Transient Dyspnea Index; TLD = targeted lung denervation.

Values are differences between 6 and 12 months and at washout visits. Pulmonary function measures were evaluated when subjects were in drug trough during the 6-month visit.

*Cycle ergometer data were collected at the 6.5- and 12.5-month time points and performed when subjects were off drugs, both at baseline and in follow-up. Values are differences between 6.5 months and the washout visit.

therapies demonstrated a 6.8% reduction in moderate to severe exacerbations and a 15% reduction in severe exacerbations (proportion of patients experiencing at least one event). These significant reductions were associated with only a -1.8-point change in SGRQ-C and a 54-ml increase in FEV₁ (3). Investigation of TLD in a larger trial (www.clinicaltrials.gov identifier NCT03639051) will explore treatment impact on secondary outcomes evaluated in this study.

The present trial confirms safety, particularly in the low number and transient nature of gastrointestinal side effects. No hemoptysis, pneumothorax, or airway changes were noted out

to 1 year in this study, consistent with longer-term follow-up of earlier trials (15, 16).

The risk of gastrointestinal side effects after TLD was recognized early in the development of the TLD procedure, and considerations have been made at each stage of development to mitigate the occurrence of these unwanted side effects (15–17). The likely cause of these gastrointestinal side effects is inadvertent damage to the vagal esophageal plexus (44–46), which runs along the outside of the esophagus near zones of RF ablation. On average, the gastrointestinal symptoms as quantified by the PAGI-SYM questionnaire are transient,

with increases seen in the post-procedural period, and are no different from those of the sham procedure by 6 months. In line with TLD, observation of transient (3–6 mo after intervention) gastric dysfunction after RF ablation is most apparent in the literature on cardiac ablation for atrial fibrillation (47–49).

Further limitations of the present study include the relatively small study size, the short time window during which the primary endpoint was assessed, and the use of investigator definitions for the respiratory adverse events used. Furthermore, owing to anatomical limitations (esophageal proximity), not all patients could receive a

full circumferential treatment, resulting in potential undertreatment. The focus of the present study was on safety, which makes the interpretation of the observed reduction in severe COPD exacerbations in the TLD group complex. Although the rate of COPD exacerbations was an *a priori* secondary endpoint with a predefined definition consistent with previous studies applying this endpoint, the study did rely on physicians to independently apply that definition to each event. With this limitation in mind and with the primary focus of the study being safety, the data on changes in COPD exacerbations in the present article were presented as secondary respiratory safety measures and not as an efficacy endpoint as it was defined in the protocol. This was done with the acceptance that a larger study is needed to more precisely determine the impact of TLD on COPD exacerbations.

One of the strengths of this study is the sham-controlled design, allowing a more accurate interpretation of events between groups and minimizing both subject and observer bias. Throughout the 1 year of follow-up, 80 (98%) of the 82 patients remained blinded. The TLD treatment group bore no radiologically visible evidence of treatment that could compromise blinding, and as an additional precaution, assessors were blinded to treatment allocation as well. We conducted this study across 16 sites in five countries, and physicians had various degrees of experience with TLD before the study. Finally, 95% of patients entered the study while receiving GOLD-recommended pharmacotherapy

(dual or triple) and maintained their baseline regimens throughout the 1-year follow-up, reducing the impact that medication changes might have on prespecified outcomes observed in this trial.

In summary, the results of the AIRFLOW-2 trial show that in the 82 patients with symptomatic COPD randomized in the present study, those patients undergoing TLD combined with optimal pharmacotherapy had fewer study-defined respiratory adverse events in the primary endpoint window and fewer hospitalizations for COPD exacerbation in the 1 year after treatment. This finding merits further larger-scale studies to substantiate the effect of TLD on exacerbation rates. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Dr. Martin Mayse, the inventor who conceived of the TLD therapy investigated in this study; the volunteer study participants; and the entire AIRFLOW-2 research team for their dedication to this trial.

AIRFLOW-2 Study Group members:

Otto-Wagner-Spital, Vienna, Austria: Dr. Arschang Valipour, Dr. Christine Abele, Dr. Irene Firlinger, Kiran Kothakuzhikal, Marina Duller; Kepler Universitätsklinikum, Linz, Austria: Prof. Bernd Lamprecht, Dr. Roland Kropfmueller, Dr. Kornelia Holzmann, Sandra Rathmeier; Charité Universitätsmedizin, Berlin, Germany: Dr. Ralf Hubner, Leonore Erdmann, Dr. Bettina Temmesfeld-Wollbrück, Dr. Christoph Ruwwe Glösenkamp; Asklepios-Fachkliniken München, Gauting, Germany: Dr. Wolfgang Gesierich, Dr. Frank Reichenberger, Christa Niehaus; Thoraxklinik,

Heidelberg, Germany: Prof. Felix Herth, Dr. Ralf Eberhardt, Dr. Daniela Gompelmann, Brigitte Rump; Ruhrlandklinik–West German Lung Center, Essen, Germany: Dr. Kaid Darwiche, Dr. Stephan Eisenmann, Ulrike Kaiser, Birte Schwarz, Ulrike Sempel; Klinikverbund Kempten-Oberallgäu, Kempten, Germany: Prof. Christian Schumann, Dr. Robert Kaiser, Dr. Kathryn Schumann-Stoiber; Universitätsklinikum, Bonn, Germany: Prof. Dirk Skowasch, Sabine Ring; CHU de Grenoble–Hôpital Michallon, Grenoble, France: Prof. Christophe Pison, Dr. Amandine Briault, Dr. Francois Arbib, Marie Jondot; CHRU de Lille–Hôpital Calmette, Lille, France: Dr. Thierry Perez, Dr. Clement Fournier, Prof. Regis Matran, Dr. Michele Catto, Dr. Nathalie Bautin, Dr. Virginie De Broucker, Dr. Marie Willemin, Dr. Anne Prevotat, Dr. Ludivine Wemeau, Dr. Alice Gicquello, Morgane Foulon, Hasna Camara; CHU de Reims–Hôpital Maison Blanche, Reims, France: Prof. Gaetan Deslee, Dr. Herve Vallerand, Dr. Sandra Dury, Delphine Gras, Margaux Bonnaire-Verdier; CHRU de Strasbourg–Nouvel Hôpital Civil, Strasbourg, France: Prof. Romain Kessler, Dr. Sandrine Hirschi, Dr. Michele Porzio, Dr. Tristan Degot, Dr. Mathieu Canuet, Dr. Armelle Schuller, Julien Stauder, Sahra Ali Azouaou; Hôpital Bichât, Paris, France: Dr. Armelle Marceau, Dr. Hervé Mal, Yolande Costa; Royal Brompton and Harefield NHS Trust London and the Chelsea and Westminster Hospital, London, United Kingdom: Prof. Pallav L. Shah, Dr. Justin Garner, Dr. Karthi Srikanthan, Cielito Caneja, Dr. John Thornton; University Medical Center Groningen, University of Groningen, Groningen, the Netherlands: Dr. Dirk-Jan Slebos, Dr. Nick Ten Hacken, Dr. Jorine Hartman, Dr. Karin Klooster, Sonja Augustijn; Academic Medical Center, Amsterdam, the Netherlands: Dr. Peter Bonta, Prof. Jouke Annema, Marianne van de Pol, Annika Goorsenberg.

References

- Albert P, Agusti A, Edwards L, Tal-Singer R, Yates J, Bakke P, *et al*. Bronchodilator responsiveness as a phenotypic characteristic of established chronic obstructive pulmonary disease. *Thorax* 2012;67:701–708.
- Klooster K, ten Hacken NH, Hartman JE, Kerstjens HA, van Rikxoort EM, Slebos DJ. Endobronchial valves for emphysema without interlobar collateral ventilation. *N Engl J Med* 2015;373:2325–2335.
- Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, *et al*.; IMPACT Investigators. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med* 2018;378:1671–1680.
- Pavord ID, Chanez P, Criner GJ, Kerstjens HAM, Korn S, Lugogo N, *et al*. Mepolizumab for eosinophilic chronic obstructive pulmonary disease. *N Engl J Med* 2017;377:1613–1629.
- Chapman KR, Hurst JR, Frent SM, Larbig M, Fogel R, Guerin T, *et al*. Long-term triple therapy de-escalation to indacaterol/glycopyrronium in patients with chronic obstructive pulmonary disease (SUNSET): a randomized, double-blind, triple-dummy clinical trial. *Am J Respir Crit Care Med* 2018;198:329–339.
- Belmonte KE. Cholinergic pathways in the lungs and anticholinergic therapy for chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2005;2:297–304. [Discussion, pp. 311–312.]
- Bleecker ER. Cholinergic and neurogenic mechanisms in obstructive airways disease. *Am J Med* 1986;81:93–102.
- Canning BJ. Reflex regulation of airway smooth muscle tone. *J Appl Physiol* (1985) 2006;101:971–985.
- Gross NJ, Skorodin MS. Role of the parasympathetic system in airway obstruction due to emphysema. *N Engl J Med* 1984;311:421–425.
- Kistemaker LE, Gosens R. Acetylcholine beyond bronchoconstriction: roles in inflammation and remodeling. *Trends Pharmacol Sci* 2015;36:164–171.
- Niewoehner DE, Rice K, Cote C, Paulson D, Cooper JA Jr, Korducki L, *et al*. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. *Ann Intern Med* 2005;143:317–326.

12. Vogelmeier C, Hederer B, Glaab T, Schmidt H, Rutten-van Mölken MP, Beeh KM, *et al.*; POET-COPD Investigators. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med* 2011;364:1093–1103.
13. Hummel JP, Mayse ML, Dimmer S, Johnson PJ. Physiologic and histopathologic effects of targeted lung denervation in an animal model. *J Appl Physiol* (1985) 2019;126:67–76.
14. Zaccone EJ, Udem BJ. Airway vagal neuroplasticity associated with respiratory viral infections. *Lung* 2016;194:25–29.
15. Slebos DJ, Klooster K, Koegelenberg CF, Theron J, Styen D, Valipour A, *et al.* Targeted lung denervation for moderate to severe COPD: a pilot study. *Thorax* 2015;70:411–419.
16. Valipour A, Asadi S, Pison C, Jondot M, Kessler R, Benneddf K, *et al.* Long-term safety of bilateral targeted lung denervation in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2018;13:2163–2172.
17. Valipour A, Shah PL, Pison C, Ninane V, Janssens W, Perez T, *et al.*; on behalf of the AIRFLOW-1 Study Group. Safety and dose study of targeted lung denervation in moderate/severe COPD patients. *Respiration* 2019;98:329–339.
18. Slebos DJ, Shah P, Herth F, Pison C, Schumann C, Kessler R, *et al.* A double-blind, randomized, sham-controlled study of targeted lung denervation in patients with moderate to severe COPD [abstract]. *Eur Respir J* 2018;52(Suppl 62):OA4929.
19. Revicki DA, Rentz AM, Dubois D, Kahrilas P, Stanghellini V, Talley NJ, *et al.* Gastroparesis Cardinal Symptom Index (GCSI): development and validation of a patient reported assessment of severity of gastroparesis symptoms. *Qual Life Res* 2004;13:833–844.
20. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, *et al.* Standardisation of the measurement of lung volumes. *Eur Respir J* 2005;26:511–522.
21. American Thoracic Society; American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167:211–277. [Published erratum appears in *Am J Respir Crit Care Med* 167:1451.]
22. Jones PW. St. George's Respiratory Questionnaire: MCID. *COPD* 2005; 2:75–79.
23. Meguro M, Barley EA, Spencer S, Jones PW. Development and validation of an improved, COPD-specific version of the St. George Respiratory Questionnaire. *Chest* 2007;132:456–463.
24. Nolan CM, Longworth L, Lord J, Canavan JL, Jones SE, Kon SS, *et al.* The EQ-5D-5L health status questionnaire in COPD: validity, responsiveness and minimum important difference. *Thorax* 2016;71:493–500.
25. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur Respir J* 2009;34:648–654.
26. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;54:581–586.
27. Witek TJ Jr, Mahler DA. Meaningful effect size and patterns of response of the transition dyspnea index. *J Clin Epidemiol* 2003;56:248–255.
28. Rentz AM, Kahrilas P, Stanghellini V, Tack J, Talley NJ, de la Loge C, *et al.* Development and psychometric evaluation of the patient assessment of upper gastrointestinal symptom severity index (PAGI-SYM) in patients with upper gastrointestinal disorders. *Qual Life Res* 2004;13:1737–1749.
29. Kerwin E, Hébert J, Gallagher N, Martin C, Overend T, Alagappan VK, *et al.* Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. *Eur Respir J* 2012;40: 1106–1114.
30. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, *et al.*; UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;359:1543–1554.
31. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA; INSPIRE Investigators. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med* 2008;177:19–26.
32. Oenema TA, Kolahian S, Nanninga JE, Rieks D, Hiemstra PS, Zuyderduyn S, *et al.* Pro-inflammatory mechanisms of muscarinic receptor stimulation in airway smooth muscle. *Respir Res* 2010;11:130.
33. Beeh KM, Burgel PR, Franssen FME, Lopez-Campos JL, Loukides S, Hurst JR, *et al.* How do dual long-acting bronchodilators prevent exacerbations of chronic obstructive pulmonary disease? *Am J Respir Crit Care Med* 2017;196:139–149.
34. Zanini A, Cherubino F, Zampogna E, Croce S, Pignatti P, Spanevello A. Bronchial hyperresponsiveness, airway inflammation, and reversibility in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2015;10:1155–1161.
35. Widdicombe JG. Overview of neural pathways in allergy and asthma. *Pulm Pharmacol Ther* 2003;16:23–30.
36. McAlexander MA, Gavett SH, Kollarik M, Udem BJ. Vagotomy reverses established allergen-induced airway hyperreactivity to methacholine in the mouse. *Respir Physiol Neurobiol* 2015;212-214: 20–24.
37. Tränkner D, Hahne N, Sugino K, Hoon MA, Zuker C. Population of sensory neurons essential for asthmatic hyperreactivity of inflamed airways. *Proc Natl Acad Sci USA* 2014;111:11515–11520.
38. Empey DW, Laitinen LA, Jacobs L, Gold WM, Nadel JA. Mechanisms of bronchial hyperreactivity in normal subjects after upper respiratory tract infection. *Am Rev Respir Dis* 1976;113:131–139.
39. Koegelenberg C, Theron J, Slebos DJ, Klooster K, Mayse M, Bolliger CT. Additive effect of targeted lung denervation plus drug in patients with COPD [abstract]. *Eur Respir J* 2015;46(Suppl 59):PA3963.
40. Casaburi R, Mahler DA, Jones PW, Wanner A, San PG, ZuWallack RL, *et al.* A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002;19: 217–224.
41. Rennard SI, Anderson W, ZuWallack R, Broughton J, Bailey W, Friedman M, *et al.* Use of a long-acting inhaled β_2 -adrenergic agonist, salmeterol xinafoate, in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;163: 1087–1092.
42. Calzetta L, Rogliani P, Ora J, Puxeddu E, Cazzola M, Matera MG. LABA/LAMA combination in COPD: a meta-analysis on the duration of treatment. *Eur Respir Rev* 2017;26:160043.
43. Wedzicha JA, Decramer M, Ficker JH, Niewoehner DE, Sandström T, Taylor AF, *et al.* Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. *Lancet Respir Med* 2013;1:199–209.
44. Banki F, Mason RJ, DeMeester SR, Hagen JA, Balaji NS, Crookes PF, *et al.* Vagal-sparing esophagectomy: a more physiologic alternative. *Ann Surg* 2002;236:324–335. [Discussion pp, 335–336.]
45. Doubilet H, Shafiroff BG, Mulholland JH. The anatomy of the periesophageal vagi. *Ann Surg* 1948;127:128–135.
46. Herbella FA, Regatieri CV, Moreno DG, Matone J, Del Grande JC. Vagal integrity in vagal-sparing esophagectomy: a cadaveric study. *Dis Esophagus* 2006;19:406–409.
47. Bunch TJ, Ellenbogen KA, Packer DL, Asirvatham SJ. Vagus nerve injury after posterior atrial radiofrequency ablation. *Heart Rhythm* 2008;5:1327–1330.
48. Kuwahara T, Takahashi A, Takahashi Y, Kobori A, Miyazaki S, Takei A, *et al.* Clinical characteristics and management of periesophageal vagal nerve injury complicating left atrial ablation of atrial fibrillation: lessons from eleven cases. *J Cardiovasc Electrophysiol* 2013;24: 847–851.
49. Lakkireddy D, Reddy YM, Atkins D, Rajasingh J, Kanmanthareddy A, Olyae M, *et al.* Effect of atrial fibrillation ablation on gastric motility: the atrial fibrillation gut study. *Circ Arrhythm Electrophysiol* 2015;8: 531–536.