Bronchial Rheoplasty for Treatment of Chronic Bronchitis
Twelve-Month Results from a Multicenter Clinical Trial

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Abstract

Rationale: Chronic bronchitis (CB) is characterized by productive cough with excessive mucus production, resulting in quality-of-life impairment and increased exacerbation risk. Bronchial rheoplasty uses an endobronchial catheter to apply nonthermal pulsed electrical fields to the airways. Preclinical studies have demonstrated epithelial ablation followed by regeneration of normalized epithelium.

Objectives: To evaluate the feasibility, safety, and initial outcomes of bronchial rheoplasty in patients with CB.

Methods: Pooled analysis of two separate studies enrolling 30 patients undergoing bilateral bronchial rheoplasty was conducted. Follow-up through 6 months (primary outcome) and 12 months included assessment of adverse events, airway histology, and changes in symptoms using the Chronic Obstructive Pulmonary Disease (COPD) Assessment Test and St. George’s Respiratory Questionnaire (SGRQ).

Measurements and Main Results: Bronchial rheoplasty was performed in all 30 patients (63% male; mean [SD] age, 67 [7.4]; mean [SD] postbronchodilator FEV1, 65% [21%]; mean [SD] COPD Assessment Test score 25.6 [7.1]; mean [SD] SGRQ score, 59.6 [15.3]). There were no device-related and four procedure-related serious adverse events through 6 months, and there were none thereafter through 12 months. The most frequent nonserious, device- and/or procedure-related event through 6 months was mild hemoptysis in 47% (14 of 30) patients. Histologically, the mean goblet cell hyperplasia score was reduced by a statistically significant amount (P < 0.001). Significant changes from baseline to 6 months in COPD Assessment Test (mean, −7.9; median, −8.0; P = 0.0002) and SGRQ (mean, −14.6; median, −7.2; P = 0.0002) scores were observed, with similar observations through 12 months.

Conclusions: This study provides the first clinical evidence of the feasibility, safety, and initial outcomes of bronchial rheoplasty in symptomatic patients with CB.

Clinical trial registered with www.anzctr.org.au (ACTRN 12617000330347) and clinicaltrials.gov (NCT 03107494).

Keywords: chronic obstructive pulmonary disease; obstructive lung diseases; respiratory tract diseases; bronchial diseases; pulsed electric field
At a Glance Commentary

Scientific Knowledge on the Subject: In chronic bronchitis (CB), chronic inflammation of the respiratory tract leads to an increased number and hyperplasia of bronchial mucus-producing cells and a mucus hypersecretion phenotype, which in turn contributes to the chronic cough and sputum production characteristic of the disease. There is an unmet clinical need for the treatment of CB. Locally acting, mucosal-ablative interventions may be useful in treating CB.

What This Study Adds to the Field: This study provides proof of concept for the safety and technical feasibility of bronchial rheoplasty, an endoscopic technique using nonthermal pulsed electrical fields to ablate airway mucosa and reduce airway mucus production in the treatment of CB. Reductions in goblet cell hyperplasia and changes in patient-reported quality-of-life measures were observed after the procedure.

Chronic obstructive pulmonary disease (COPD) is a major public health problem that is projected to rank fifth worldwide in terms of disease burden and third in terms of mortality (1). The predominant subtypes of COPD include emphysema and chronic bronchitis (CB). CB is defined as chronic cough and sputum production for 3 mo/yr for 2 consecutive years. The pathophysiology of CB is chronic inflammation of the respiratory tract, leading to overproduction and hypersecretion of mucus together with impaired mucociliary clearance (2–4).

As a result, patients with CB report symptoms such as persistent cough, production of phlegm, and/or shortness of breath. The diagnosis of CB is associated with more frequent and severe exacerbations, quality-of-life impairments, and increased morbidity and mortality (5–11). The prevalence of CB in the adult population ranges from 3.4% to 22.0%, depending on the definition used, and affects smokers with and without COPD (12, 13). In fact, previous studies suggest that symptoms of CB may predict the development of COPD (13–16).

Despite the impact of CB on morbidity and mortality, little progress has been made in developing effective therapies. Common therapies in managing COPD, including inhaled β2-agonists, anticholinergics, and glucocorticoids, have either not been studied specifically in the CB subtype or have yielded conflicting results (12). Roflumilast (a phosphodiesterase-4 inhibitor) has been shown to be effective in treating CB, but side effects limit its use in clinical practice (17, 18). Despite guideline-directed therapy, many patients with CB remain significantly symptomatic.

Bronchial rheoplasty is a procedure that uses nonthermal pulsed electrical fields with the intention of ablating the abnormal mucus-producing cells of the airway epithelium, thereby allowing normal, healthy epithelial regeneration to occur. The current study evaluates the technical feasibility, safety, and initial outcomes of this therapy in patients with CB. Some of the results of this study have been previously reported in the form of abstracts (19–21).

Methods

Study Design

Two prospective, multicenter, single-arm clinical studies under two nearly identical protocols, differing mainly by local specifications and requirements (Australia: ACTRN 12617000330347; Austria and Chile: NCT 03107494), were conducted in patients with diagnosed CB. The study informed-consent forms were approved by the local ethics committee at each study center. All patients provided written informed consent before screening.

Patients were recruited at five tertiary academic centers in Australia, Austria, and Chile between February 2017 and October 2018. The study population included adult patients who were at least 40 years of age and had a smoking history of at least 10 pack-years, with CB defined as a productive cough for 3 months in each of 2 successive years, and in whom other causes of productive cough had been excluded. The initial protocol required patients to have a post-bronchodilator FEV1 of ≥30% and ≤80% of predicted volume within 3 months of enrollment, together with a FEV1/FVC ratio < 0.70. Early during the enrollment period, however, it was noted that there was a significant number of patients suffering from significant CB symptoms who had relatively normal lung function (FEV1/FVC ratio ≥ 0.7 or FEV1 ≥ 80%) but otherwise appeared to be good candidates for bronchial rheoplasty. The protocol was amended to remove the FEV1/FVC ratio criterion and to allow enrollment of patients with FEV1 ≥ 80% if they had a COPD Assessment Test (CAT) total score ≥ 10 and the first two items on their CAT (“I never cough” vs. “I cough all the time” and “I have no phlegm in my chest at all” vs. “My chest is full of phlegm”) summed to a score ≥7 points.

Exclusion criteria included oral steroid–dependent conditions (>10 mg/d), active respiratory infection, COPD exacerbation within 6 weeks before treatment, abnormal cardiac rhythm at the time of the first procedure, history of arrhythmia within the past 2 years, presence of implantable cardiac devices, prior lung surgery, history of asthma before age 30, and current smoking (within 6 mo of treatment). See the complete listing of entry criteria in the online supplement.

Patients were to be maintained on stable pharmacologic treatment regimens throughout the study follow-up.

Bronchial Rheoplasty System Description

The RheOx System (Gala Therapeutics) consists of an electrosurgical generator and a single-use catheter (see Figure E1 in the online supplement). The system is designed to deliver pulsed electrical fields (high-frequency, short-duration, nonthermal electrical fields) to the airway epithelium and mucosa. This targeted energy delivery is intended to cause cell death by disrupting cellular homeostasis, leading to processes such as osmotic swelling and apoptosis (19–21). This cell death does not destroy the architectural function of the tissue, permitting subsequent regeneration of normalized epithelium and a reduction in airway mucus production. Additional detail on the RheOx System is provided in the online supplement.

Procedure Description

The procedure is performed under general anesthesia through a bronchoscope with at least a 2.8-mm working channel. Once the bronchoscope is in place, the endobronchial catheter is inserted and delivered to the target location in the airway, and the
slides were reviewed by a board-certified anatomic pathologist with subspecialty expertise in pulmonary pathology. The pathologist graded the degree of epithelial goblet cell hyperplasia using a prespecified, semiquantitative methodology consisting of a categorical scale, described in detail in Figure E2. The pathologist was blinded to the patient identification and to the time point of the sample collection.

Outcomes
The primary outcome of the study was safety, as assessed by the incidence and evaluation of serious adverse events (SAEs) associated with the device through 6 months. Safety was also assessed by evaluating the type, frequency, and severity of nonserious adverse events (AEs), their potential relationship to the study device or procedure, and their timing in relation to the treatment. Events were defined as occurring during the treatment recovery period if they occurred within 30 days of either treatment. Events thereafter were defined as occurring during the 3-, 6-, or 12-month periods after the second treatment, excluding the treatment recovery period. Spirometry testing (FEV$_1$ and FVC) was incorporated as an additional safety measure.

Further outcomes included evaluation of the effects of bronchial rheoplasty on goblet cell hyperplasia score and disease-related symptoms and quality of life using CAT and St. George’s Respiratory Questionnaire (SGRQ) total scores. Goblet cell hyperplasia was assessed at 3 months after the second procedure. CAT and SGRQ scores were collected at baseline and at 3, 6 (primary assessment), and 12 months after the second procedure visit, and responder rates were calculated using 2-point and 4-point thresholds for CAT (22) and SGRQ (23), respectively.

Statistical Methods
Because this was a safety and feasibility study, no formal sample-size calculation was performed. Descriptive statistics and graphical representations were used to summarize the data. For categorical variables, counts and percentages were calculated. For continuous variables, means, medians, quartiles, SDs, and, when appropriate, 95% confidence intervals for the mean, assuming a normal distribution, were calculated. All calculations were based on available data; no imputations or extrapolations were used to replace missing values. P values for longitudinal secondary outcome measures (CAT and SGRQ) at baseline and 3, 6, and 12 months were computed using a nonparametric test appropriate for repeated measures (Friedman’s test) (24), followed by pairwise Wilcoxon signed rank tests of changes from baseline, with a Hochberg adjustment for
multiplicity. Data analyses were performed using SAS version 9.4 (SAS Institute).

### Results

Forty-two patients were screened, and 30 patients were enrolled (Table E2). Follow-up to 6 and 12 months after the second study treatment was available for 30 and 29 out of 30 patients, respectively (Figure 1).

Enrolled patients had a mean (SD) FEV\textsubscript{1} % predicted of 65% (21%), CAT score of 25.6 (7.1) points, and SGRQ score of 59.6 (15.3) points, indicating a high symptom burden, despite most patients being on inhaled long-acting bronchodilator treatment and nearly half of patients being on inhaled corticosteroid therapy (Table 1). The medication regimen at study entry was maintained through the 12-month follow-up in 27 of the 30 patients. Two patients transitioned from short-acting bronchodilator inhaler therapy to long-acting bronchodilator treatment with inhaled corticosteroid therapy per the treating physician’s recommendation, and one patient had his long-acting antimuscarinic antagonist bronchodilator inhaler therapy withdrawn at the 3-month visit.

### Procedural Results and Feasibility

Bilateral bronchial rheoplasty was completed in all 30 enrolled patients (60 procedures), with successful catheter deployment and energy delivery to the target sites in all procedures. A mean (SD) of 43 (21) activations were applied per lung. The median post-procedure hospital stay was 1 day (range, 0–4). In 92% of procedures, patients were discharged within 48 hours of the procedure. Figure 2 shows bronchoscopic images taken before and after bronchial rheoplasty in a representative patient.

### Primary Study Outcome and Additional Safety Assessments

No device-related SAEs and four procedure-related SAEs were reported through 6 months, with no additional device- or procedure-related SAEs in the 6- to 12-month period. Three of the four procedure-related SAEs occurred during the treatment recovery period, including one case of pneumonia 2 days after the procedure; one case of mucosal scarring observed at the second bronchoscopy, which was determined to have been related to cryobiopsy sampling during the first bronchoscopy procedure; and one case of COPD exacerbation, which started the same day as the second procedure. The fourth procedure-related SAE was a COPD exacerbation that occurred the day of the third bronchoscopy, which was for research only.

### Table 1. Patient Demographics, Baseline Clinical Characteristics, and Medications

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (N = 30 Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>67 (7.4)</td>
</tr>
<tr>
<td>Sex, M, n (%)</td>
<td>19 (63.3)</td>
</tr>
<tr>
<td>BMI, kg/m\textsuperscript{2}</td>
<td>27.5 (4.7)</td>
</tr>
<tr>
<td>Smoking history, pack-years</td>
<td>40.7 (26.5)</td>
</tr>
<tr>
<td>FEV\textsubscript{1} % predicted*</td>
<td>65.0 (21.2)</td>
</tr>
<tr>
<td>FEV\textsubscript{1}/FVC ratio*</td>
<td>0.53 (0.14)</td>
</tr>
<tr>
<td>Airflow obstruction, n (%)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>CB w/o airflow obstruction</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>GOLD I</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>GOLD II</td>
<td>9 (30.0)</td>
</tr>
<tr>
<td>TLC% predicted*</td>
<td>111.6 (14.2)</td>
</tr>
<tr>
<td>RV% predicted*</td>
<td>142.2 (39.8)</td>
</tr>
<tr>
<td>RV/TLC*</td>
<td>48.7 (10.1)</td>
</tr>
<tr>
<td>Emphysema, % (−950 HU)</td>
<td>8.0 (9.2)</td>
</tr>
<tr>
<td>6MWT, m\textsuperscript{†}</td>
<td>443.2 (92.4)</td>
</tr>
<tr>
<td>CAT total score</td>
<td>25.6 (7.1)</td>
</tr>
<tr>
<td>CAT phlegm score</td>
<td>4.1 (0.8)</td>
</tr>
<tr>
<td>CAT cough score</td>
<td>3.6 (0.9)</td>
</tr>
<tr>
<td>SGRQ total score</td>
<td>59.6 (15.3)</td>
</tr>
<tr>
<td>SGRQ symptoms score</td>
<td>76.1 (13.4)</td>
</tr>
<tr>
<td>Inhaled pharmacologic treatment, n (%)</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>LABA/LAMAVICS, LABA/LAMA, LABA only, LAMA only</td>
<td>27 (90.0)</td>
</tr>
<tr>
<td>ICS only</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Oral roflumilast, n (%)</td>
<td>3 (10)</td>
</tr>
</tbody>
</table>

*One patient did not have post-bronchodilator pulmonary-function testing done (protocol deviation).
†Three patients did not perform the 6MWT.

**Definition of abbreviations:** 6MWT = 6-minute-walk test; BMI = body mass index; CAT = Chronic Obstructive Pulmonary Disease Assessment Test; CB = chronic bronchitis; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HU = Hounsfield units; ICS = inhaled corticosteroids; LABA = long-acting β-agonist bronchodilator; LAMA = long-acting muscarinic antagonist bronchodilator; RV = residual volume; SGRQ = St. George’s Respiratory Questionnaire; w/o = without.

Data are mean (SD) unless otherwise noted. Lung-function parameters are after bronchodilator therapy. The images show the endoscopic view of the left upper lobe carina with both upper and lower lobe airways visible.
Other than the 4 procedure-related SAEs described above, 12 SAEs unrelated to either device or procedure were reported in nine patients through 12 months (Table 2). The most frequently reported SAE was COPD exacerbation (13.3%, 4 of 30 patients). There was one case of atrial fibrillation 1 week after the procedure, judged by the investigator to be unrelated to the procedure or device but instead related to an unreported preexisting condition exacerbated by alcohol consumption. This event resolved without sequelae 1 day later after prescription of an intravenous β-blocker. No acute cardiac rhythm abnormalities occurred during the procedure in any patient. One patient died of end-stage COPD, unrelated to either the device or the procedure, 381 days after the second procedure.

Nonserious device-related and procedure-related AEs through 12 months are presented in Tables E3 and E4, respectively. The majority (85%) of these events occurred during the treatment recovery period. The most frequent nonserious AEs that were device and/or procedure related were COPD exacerbations (30%, 9 of 30 patients), which were generally moderate in severity and successfully treated with antibiotic and/or systemic steroid therapy; mild hemoptysis (47%, 14 of 30 patients); and sore throat (33%, 10 of 30 patients). All hemoptysis events resolved spontaneously without any intervention or follow-up required. No unexpected AEs related to the device or procedure were reported during the study.

Moderate and severe COPD-exacerbation event rates during the study, defined as the number of events per patient-year of follow-up, were 1.20 (SD, 1.30) and 0.21 (SD, 0.60), respectively.

There were no statistically significant changes in lung-function parameters (FEV1, FVC) at 3, 6, or 12 months after the procedure compared with baseline.

**Histological Assessments**

A representative example of the histological changes between the pre- and post-treatment biopsies shows marked goblet cell hyperplasia of the right bronchus intermedius at baseline (Figure 3A, score = 2), followed by a 1-point reduction (i.e., improvement) in goblet cell hyperplasia from the same location at the 3-month follow-up bronchoscopy (Figure 3B, score = 1).

Overall, 54 matched sets (baseline and follow-up) of histological samples were available for analysis. In six lungs, one or more of the samples demonstrated insufficient material for further analysis. The mean (SD) goblet cell hyperplasia score was reduced from 1.48 (0.91) at baseline to 0.91 (0.81) after treatment, a relative reduction of 39% (P < 0.001; Table 3). Of the 25 matched lung biopsies with baseline goblet cell hyperplasia scores of 2 or 3 (indicating a moderately or severely increased ratio of goblet cells to ciliated bronchial epithelial cells, respectively), 21 (84%) were reduced by at least 1 point after treatment (Table 4).

**Symptoms and Quality-of-Life Assessments**

Statistically significant changes in health-related quality-of-life outcomes were observed at 3, 6, and 12 months after the second treatment (Figure 4 and Table E5). At the 6-month primary assessment, the median (interquartile range) changes from baseline in CAT and SGRQ total scores were −8.0 (−14.0 to −2.0) points (P = 0.0002) and −7.2 (−19.8 to −3.1) points (P = 0.0002), respectively, and mean (SD) changes from baseline were −7.9 (8.3) points and −14.6 (19.4) points, respectively. Responder rates for the CAT and SGRQ at 6 months were 76.7% and 70.0%, respectively. At the 12-month follow-up, median (interquartile range) changes from baseline in CAT and SGRQ were −8.0 (−14.0 to 1.0) points and −14.7 (−27.8 to −2.0) points, respectively, and mean (SD) changes from baseline were −7.0 (8.9) points and −15.2 (20.4) points, respectively. Responder rates for the CAT and SGRQ at 12 months were 69% (20 of 29) and 72% (21 of 29), respectively.

*Post hoc* analyses of 6-month component scores from the CAT and SGRQ questionnaires showed reductions in CAT cough and phlegm scores (questions 1 and 2), and in all three SGRQ domains (Table E5). Individual patient changes from baseline to 6 months in CAT and SGRQ scores are also provided in Figure E3.

**Discussion**

Bronchial rheoplasty is an endoscopic technique that uses nonthermal pulsed electrical fields to ablate the airway mucosa and mucus-producing cells of the airway epithelium. On the basis of preclinical research in animals, the local extracellular matrix is left intact after the procedure (19-21), which is believed to promote healthier regeneration of the epithelium.

This initial study of bronchial rheoplasty demonstrated that the procedure is technically feasible, with an acceptable safety profile. Pulsed electrical fields were delivered from the main bronchus to the subsegmental airways, the airways most likely to contain goblet cells. The histological findings appear to confirm the proposed mechanism of action, demonstrating a statistically significant reduction in the number of epithelial goblet cells, particularly in those patients with pretreatment evidence of moderate-to-severe goblet cell hyperplasia. These observations were accompanied by statistically significant reductions in CAT and SGRQ scores through 12 months.

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The above findings were observed in the presence of an acceptable safety profile. No patients experienced a device-related SAE, and four patients experienced a procedure-related SAE, each of which resolved without sequelae. No device- or procedure-related SAEs were observed beyond 3 months. Given that the RheOx System delivers high-voltage energy to the airways in close proximity to the heart, monitoring for cardiac arrhythmias was of particular interest in characterizing safety. No acute cardiac rhythm abnormalities occurred during the procedure in any patient. One patient developed atrial fibrillation 1 week after the procedure, which was, however, considered to be unrelated to the device or procedure. This patient failed to report a history of prior atrial fibrillation, which may have been exacerbated by general anesthesia, the procedure, and/or the patient’s behavior (i.e., significant alcohol consumption).

There was a 30% rate of nonserious, moderate COPD exacerbations during the treatment recovery period. The overall rates of moderate and severe COPD exacerbations in the present study were 1.20 and 0.21 events per patient-year, respectively. These rates appear to be similar to those of a cross-sectional analysis of 112 French patients with COPD and a CB phenotype, in which reported moderate and severe COPD exacerbation rates were 1.80 and 0.43 events per patient-year, respectively (25). Nevertheless, we acknowledge that the occurrence of COPD exacerbations may in part have been influenced by the bronchoscopic interventions, which included multiple cryobiopsies. To put this rate into context, an analysis of the SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study) trial demonstrated a 27% rate of respiratory complications after research bronchoscopy performed in patients with COPD (26).

Spirometry was performed primarily for safety reasons and was unaffected by the procedure. Given the absence of a relationship between goblet cell density and classic markers of lung function (FEV1 and FVC) in a previous report (27), we did not expect to observe substantive changes in these measures. Improvements in CB symptoms may better correlate with small airway function and are better measured with impulse oscillometry, body plethysmography, and/or computed tomography–derived parameters, such as airway count and/or airway volumes (28–30).

Few other interventional device systems have been developed to ablate the abnormal airway epithelium and mucosa in patients with obstructive airway disease. In contrast to bronchial rheoplasty, these systems deliver thermal energy to achieve changes in airway pathology. Bronchial thermoplasty is a U.S. Food and Drug Administration–approved procedure that uses radiofrequency energy to reduce airway smooth muscle mass through bronchoscopy to all visible airways. Clinical benefits accompanied by histological changes underlying the mechanism of

### Table 2. Serious Adverse Events

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Treatment Recovery Period* (n Events)</th>
<th>3 mo† (n Events)</th>
<th>6 mo‡ (n Events)</th>
<th>12 mo§ (n Events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device-related</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Procedure-related</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD exacerbation</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mucosal scarring</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unrelated to device or procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>COPD exacerbation</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Erysipelas</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Femoral artery stenosis</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lung nodule</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal injury</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**Definition of abbreviation:** COPD = chronic obstructive pulmonary disease.

There were a total of 16 events in 11 patients. One patient experienced 2 COPD exacerbations in separate time intervals.

*Thirty days after either bronchial rheoplasty procedure.
†Follow-up period through 3 months after treatment 2, excluding either treatment recovery period.
‡Follow-up period between 3 months and 6 months after treatment 2.
§Follow-up period between 6 months and 12 months after treatment 2.

### Table 3. Histopathology Results: Goblet Cell Hyperplasia Scores

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (lungs biopsied)</td>
<td>54</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Mean score (SD)</td>
<td>1.48 (0.91)</td>
<td>0.91 (0.81)</td>
<td>−0.57*</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.23 to 1.73</td>
<td>0.69 to 1.13</td>
<td>−0.83 to −0.32</td>
</tr>
</tbody>
</table>

**Definition of abbreviation:** CI = confidence interval.

Table presents changes from baseline to 90 days and 120 days after the procedure for the left and right lungs, respectively. One biopsy sample is assessed for each lung at each of the two time points (baseline and follow-up).

*P < 0.001.
action have been demonstrated in patients with refractory asthma, in the presence of significant procedure- and device-related side effects after treatment (31). Bronchial thermoplasty, however, has not yet been studied in COPD.

More recently, metered cryospray therapy has been introduced to ablate airway mucosa in patients with CB. Five out of 11 patients scheduled to undergo surgery for lung cancer underwent this endoscopic approach, followed by lung resection and assessments of airway histology at 2 weeks (32). Similar to findings in the present study, reepithelialization at the treatment site was observed in that report. However, because of the lack of published safety, histology, and outcome data beyond 2 weeks, it is not possible to draw further conclusions or otherwise compare these current technologies.

With any new interventional technique, however, careful patient selection is one of the most important considerations. Patients were selected for this study using a high CB symptom threshold, as determined by the first two items of the CAT instrument (cough and phlegm or mucus). Although there is no agreed-on method for staging patients with CB, several definitions have been used (27, 33), and higher scores on the first two CAT items have been correlated with worse quality-of-life scores, lower FEV1 and FVC, worse computed tomography–derived airway parameters,

### Table 4. Goblet Cell Hyperplasia Score: Change by Baseline Score

<table>
<thead>
<tr>
<th>Baseline Goblet Cell Hyperplasia Score* (N=54 Airway Biopsies)</th>
<th>Improved</th>
<th>No Change</th>
<th>Worsened</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Table presents changes from baseline to 90 days and 120 days after the procedure for the left and right lungs, respectively. One biopsy sample is assessed for each lung at each of the two time points (baseline and follow-up).

*Graded on a 4-point scale in which 0 = normal ratio of goblet cells to ciliated bronchial epithelial cells (1 goblet cell per 10 or more bronchial epithelial cells); 1 = mild goblet cell hyperplasia (1 goblet cell per approximately 3–10 ciliated bronchial epithelial cells); 2 = moderate goblet cell hyperplasia (approaching 1 goblet cell per ciliated bronchial epithelial cell); and 3 = severe goblet cell hyperplasia (>1 goblet cell per ciliated bronchial epithelial cell).

![Figure 4](image-url)

**Figure 4.** Quality-of-life outcomes. The 3-, 6-, and 12-month time points are in relation to the second treatment procedure. Box plots indicate minimum, first-quartile, median (solid horizontal line), third-quartile, and maximum values. Diamonds indicate mean values. (A) Total CAT score. (B) Total SGRQ score. CAT = Chronic Obstructive Pulmonary Disease Assessment Test; SGRQ = St. George’s Respiratory Questionnaire.
and more frequent COPD-related hospitalizations (33). In our study, the final protocol versions did not require a COPD diagnosis based on pulmonary function tests. Patients with preserved lung function were allowed if they met other study criteria, including the CB symptom thresholds. During the enrollment phase, we identified a significant number of patients suffering from significant CB symptoms who had relatively normal lung function (FEV1/FVC ratio ≥ 0.7) and were thus deemed to be good candidates for bronchial rhaphoplasty. This is consistent with recent studies that have shown that smokers and former smokers with chronic respiratory symptoms of chronic mucus hypersecretion, cough, and dyspnea, but relatively normal spirometry, constitute a significant proportion of clinical consultations (13, 34) and that these individuals may have early stages of COPD not yet evidenced by airflow limitation (35), representing a significant unmet clinical need. Çolak and colleagues (13) also showed that chronic respiratory symptoms are associated with respiratory hospitalizations and death in individuals with normal spirometry.

As an initial safety and feasibility study, this study had limitations that included a small sample size and lack of a control group. Although the observed changes in airway histology and the observed findings in CAT and SGRQ scores suggest a treatment effect warranting further investigation, we cannot rule out the potential influence of an intervention or placebo effect on patient-reported outcomes. In a randomized controlled trial of targeted lung denervation in patients with moderate-to-severe COPD, mean changes in SGRQ of −3.8 and −2.5 points at 6 and 12 months were observed, respectively, in the group of patients who underwent sham bronchoscopy (36). Similar results have been reported in other blinded studies evaluating endoscopic interventions in COPD, with changes in CAT and SGRQ data with bronchoscopy alone in the range between 0 and −3.7 points (37, 38). Additional limitations of the current study are that the goblet cell hyperplasia scoring was performed by a single pathologist and that the semiquantitative scale has not been validated. Furthermore, given the sample size of the current study, we were not able to calculate an intrarater variability of the histological reads. A randomly selected subset of 20 of the 54 samples were, however, regraded by the pathologist in a blinded fashion, resulting in a similarly statistically significant reduction of the goblet cell hyperplasia score (P = 0.0013, data not shown). That said, and though no standardized scoring system has been developed for assessing changes in airway biopsy samples in CB, a similar 4-point scale was employed by Gordon and colleagues (39) when assessing goblet cell hyperplasia in biopsy samples collected from asthma patients treated with bronchial thermoplasty. Moreover, previous reports have shown that goblet cell density—a comparable measure to the one used in our study—in endobronchial biopsy samples correlated well with smoking history (3, 27) and was better at discriminating mucosal pathology than mucin-volume density (27). Other established markers of submucosal gland hypertrophy, such as the Reid Index, failed to show any differences between those with CB and those without (40, 41) and were therefore not used. Finally, it is not known whether a bilateral treatment during a single procedure would potentially decrease the total risk of procedure-related events by reducing the number of airway interventions.

In summary, this study provides the first clinical evidence of the feasibility, safety, and initial outcomes of bronchial rhaphoplasty in symptomatic patients with CB.

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