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SHORT REPORT

Bronchial Rheoplasty for Chronic Bronchitis: Results from a Canadian Feasibility Study with RheOx®

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Purpose: Chronic bronchitis (CB), a chronic obstructive pulmonary disease (COPD) phenotype defined by persistent mucus hypersecretion and cough, is associated with poor quality of life, exacerbations, and lung function impairment. Bronchial Rheoplasty (BR) delivers non-thermal pulsed electric fields to airway epithelium and submucosa. Preliminary studies demonstrated reduced airway goblet cell hyperplasia and symptom improvement in response to BR. This study aimed to further assess the safety and clinical feasibility of BR in the setting of CB.

Patients and Methods: This 3-center, single-arm study evaluated the safety and feasibility of BR in Canadian patients. The major inclusion criteria were the sum of CAT first 2 questions (cough and mucus) ≥ 7 out of 10 and FEV_1 ≥ 30% predicted. Right-sided airways were treated first; left, 1 month later. Serious adverse events (SAEs) were tabulated through 12 months. Outcomes were evaluated using the SGRQ and CAT.

Results: Ten patients with CB were enrolled and followed for 12 months. The BR procedure was successful in all patients (mean age 69 ± 5.8 years, post-BD FEV_1 77.1 ± 28.3, SGRQ 56.2 ± 8.8, CAT 25.4 ± 4.7). Only one SAE, a COPD exacerbation 13 days following the BR procedure, was considered device related. No additional SAEs occurred through 12 months, and 90% of the patients were CAT responders (≥ 2-point improvement) at 3 and 6 months. Similar results were observed in SGRQ.

Conclusion: BR was safe and well-tolerated. Meaningful symptom improvement was observed through 12 months, suggesting BR may be a viable treatment option for patients with CB.

Keywords: chronic bronchitis, COPD, bronchoscopy, pulsed electric fields

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous disease, characterized by chronic airway inflammation and destruction of adjacent alveoli and vasculature. Symptoms range from chronic productive cough, wheezing, and fatigue to debilitating dyspnea. Patients' symptomatology and experience over the course of disease can vary from years of stability to acute exacerbations and respiratory failure.[1] COPD currently ranks third worldwide in terms of disease burden and is a major cause of mortality with emphysema and chronic bronchitis (CB) as the predominant phenotypes.[2] Patients with COPD often present with different combinations and degrees of symptoms particularly as the disease progresses.

The presence of cough and sputum is associated with multiple clinical consequences in COPD, including poorer health-related quality of life, increased lung function decline, risk of exacerbations, and increased all-cause mortality.[3–6] The goal of COPD therapy is traditionally targeted towards symptom management, reduction of hyperinflation in emphysema patients, and to address the frequency and severity of exacerbations with both pharmacologic and non-pharmacologic therapies available at different stages of the disease.[7] However, none of the available pharmacologic

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therapies specifically target the entirety of the secretory component of the airway mucosa which is a hallmark of the chronic bronchitis phenotype.[8,9] A therapeutic modality delivered directly to the airway mucosa to reduce the hypersecretory constituents of the airway mucosa while encouraging a reformative-type of injury response may result in the restoration of the function of the diseased airway tissue. In that context, it may also improve quality of life and perhaps slow the decline in lung function with the potential to reduce exacerbation frequency, duration, and severity.

Bronchial rheoplasty (BR) using RheOx® (Galvanize Therapeutics, Redwood City, CA, USA), was designed specifically to target the airway inflammation and mucus hypersecretion that defines the CB phenotype.[10–12] Bronchial Rheoplasty (BR) uses pulsed electric fields (PEF) to treat abnormal airway mucosa inclusive of the hyperplastic cellular component of the mucosa with limited impact on the extracellular matrix.[13] In theory, this should allow for re-epithelialization restoring a more "normal" distribution of the various cellular constituents of the tissue including a reduction in goblet cells.[10,12] To date, the therapy has demonstrated a robust safety profile along with both clinically meaningful improvements in symptom burden through 12 months and significant reductions in goblet cell hyperplasia (GCH) on histologic evaluations of airway mucosal biopsies.[12] Herein, we present data from a prospective, 3-center, single-arm feasibility study performed in Canada to further assess the safety and clinical feasibility of bronchial rheoplasty in patients with CB. This study builds on findings from the first in human study[12] with the intent of providing further evidence to support the hypothesis that BR is safe and results in clinically meaningful improvements in patient quality of life.

Materials and Methods

Study Design

A prospective, single-arm feasibility study was conducted to assess the safety and clinical utility of bronchial rheoplasty in patients with CB in Canada (NCT03385616), and patients were enrolled between September 2018-September 2019. The study was conducted under the authority of the site's Ethics Committees (UBC-PHC Research Ethics Board, St. Paul's Hospital; Comite d'ethique de la recherche of the Centre Hospitalier de l'Universite de Montreal (CHUM) and the Institut Universitaire de Cardiologie et Pneumologie de Quebec (IUCPQ)), applicable local regulations, ICH GCP guidelines, and the Declaration of Helsinki. All patients provided written informed consent prior to screening. See Supplementary Table 1 for the study eligibility criteria.

Technical details of the BR procedure have been previously described.[12] In this study, patients received BR treatment in two bronchoscopic sessions, the first to treat the right lung and a second to treat the left lung approximately 4 weeks later, when the patient was due for follow up to initial treatment. Figure 1 shows the catheter in an airway.

Patients were followed 1-week and 1-month after initial treatment and at 1-week and 3, 6, and 12 months after the second treatment. Physical exam, spirometry, body plethysmography, six-minute walk test (6MWT), CBC, and CT scan were completed during the follow up period (see Supplementary Table 2). Quantitative CT analysis was performed by

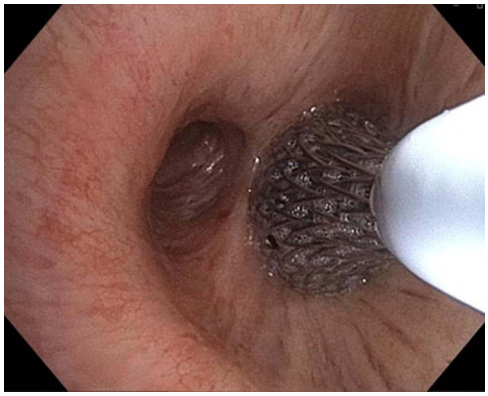

Figure 1 Representative example of the expanded RheOx Catheter. Bronchoscopic view of the RheOx Catheter positioned at the take-off of the right lower lobe with the basket deployed and with good approximation to the surrounding airway mucosa circumferentially.

FLUIDDA, Inc. (Kontich, Belgium). Questionnaires administered were COPD Assessment Test (CAT), St. George's Respiratory Questionnaire (SGRQ), and Cough and Sputum Assessment Questionnaire (CASA-Q). Airway mucosal biopsies were also collected from the majority of patients (7/10) for comparison pre- and post-treatment with BR. The methods of tissue acquisition and tissue assessment/analysis are outlined further in the Supplementary Methods and in Figure 2.

Data Analysis

The primary study outcome was safety, as assessed through analysis of serious adverse events (SAE) associated with RheOx through 6 months. With respect to the secondary outcomes, assessments were made around: pulmonary function testing (PFTs) including lung volumes and diffusing capacity (DLCO), quality of life (SGRQ, CAT, 6MWT), assessment of exacerbations, as well as procedural success (device performance). Additionally, an imaging-based assessment of changes in distal airway volume as defined as the segmented airway volume starting from the third bifurcation (4th generation) and extending distally, which include segmental bronchi and subsegmental bronchi that are discernible on the CT scan (bronchi with a diameter ~1-2mm). Assessments of changes to the airway mucosa were also evaluated (Figure 2 and Supplementary Methods).

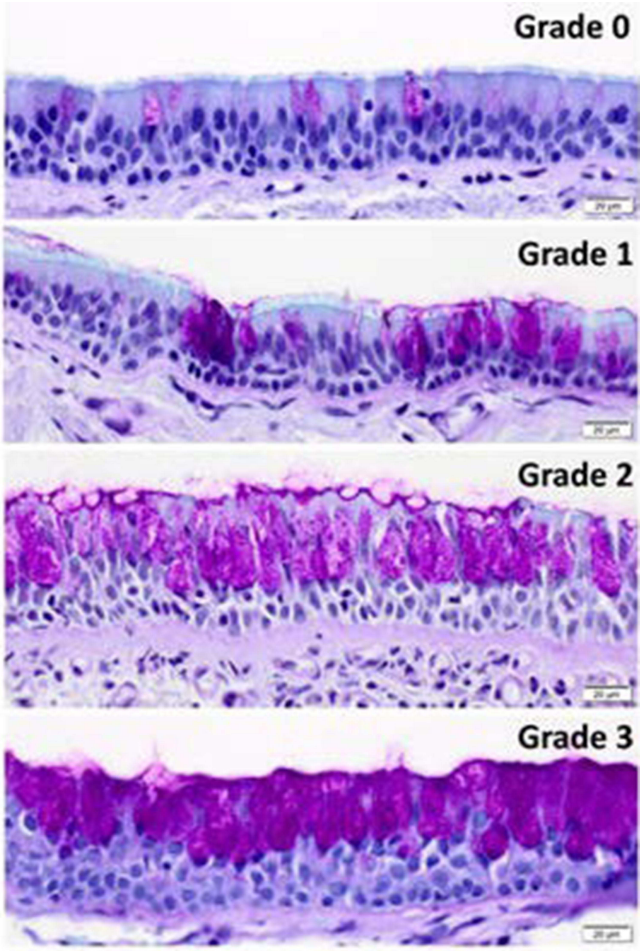

Figure 2 Goblet Cell Hyperplasia (GCH) Grading Scale. The degree of GCH was assessed in each sample and scored according to a 4-point scale, with representative images of each grade shown. Grade 0 (normal): normal numbers of goblet cells. Grade 1 (mild): moderately increased numbers of goblet cells, but less than a 1:1 ratio of goblet cells to ciliated bronchial epithelial cells. Grade 2 (moderate): significantly increased goblet cells, with approximately a 1:1 ratio of goblet cells to ciliated bronchial epithelial cells. Grade 3 (Severe): Dramatically increased numbers of goblet cells, with a ratio exceeding 1:1 of goblet cells to ciliated bronchial epithelial cells. Goblet cells are typified by the magenta cytoplasmic vacuoles seen in the most superficial epithelial layer.

Statistical Considerations

This was a prospective, single arm early feasibility study designed to assess the safety and feasibility of bronchial rheoplasty (BR) in patients with chronic bronchitis and thus formal sample size calculations were not undertaken. Descriptive statistics and graphical representations are used to summarize the data. Categorical data were calculated in frequency distributions and continuous data were summarized using mean, standard deviations, medians, minimums, and interquartile ranges. All calculations were based on available data; no imputations or extrapolations were made to replace the missing values. The creation of analysis datasets and all statistical analyses were performed using SAS version 9.4 (SAS Institute).

Results

A total of 10 patients were enrolled at 3 centers and received both BR treatments (total of 20 procedures performed in the study). All patients completed the study, with no withdrawals or deaths prior to study completion.

Baseline demographics, clinical characteristics and COPD medications are presented in Table 1. Mean (SD) age was 69.3 (5.8), smoking history of 47.3 (28.5) pack-years with baseline Post-BD FEV1% predicted of 77.1 (28.3), CAT Total Score of 25.4 (4.7), SGRQ Total Score of 56.2 (8.8). Ninety percent of the patients were receiving treatment with long-acting beta-agonists (LABA) and/or long-acting muscarinic antagonists (LAMA) and 70% with inhaled corticosteroids. Of the 10 treated patients, 2 (20%) were Global Initiative for Obstructive Lung Disease (GOLD) Stage I, 4 (40%) were GOLD Stage II, 2 (20%) were GOLD Stage III, and 2 (20%) enrolled without classically defined FEV1/FVC > 0.7. All patients tolerated both BR procedures well with a mean (SD) of 57.8 (18.6) activations applied per lung.

Only one SAE was deemed possibly related to the investigational device and procedure, a COPD exacerbation reported 13 days after the initial procedure, which required hospitalization. No unanticipated adverse events were reported. Five non-serious events were deemed possibly or probably related to the device and are summarized along with the 11 non-serious procedure-related events in Supplementary Table 3.

COPD exacerbations were defined as acute (within 48 hours of treatment) or non-acute (between 48 hours and end of study). A total of nine exacerbations occurred in three patients through 12 months follow-up. Of these, one occurred during the treatment recovery period, defined as 30 days following either BR procedure. There were no exacerbations reported during the 48-hour period immediately following either of the two bronchial rheoplasty procedures. Three of the nine exacerbations were serious.

Changes in symptom burden were assessed using the CAT, SGRQ, and CASA-Q. The minimal clinically important difference (MCID) for the CAT is a change of 2 points.[14] This change was reached in 9 of 10 patients at 3 months, 9 of 10 patients at 6 months, and 7 of 10 patients at 12 months (Figure 3). Mean (SD) changes from baseline in total CAT score were −10.0 (8.2), −10.0 (8.6), and −8.6 (9.3) at Months 3, 6 and 12, respectively. The MCID for SGRQ is a change

Table 1 Baseline Demographics, Clinical Characteristics and Medications

Characteristic	N=10 Patients
Age	69.3 (5.8)
Male; n (%)	5 (50%)
BMI	30.6 (7.4)
Smoking History (Pack-years)	47.3 (28.5)
FEV_1% Predicted*	77.1 (28.3)
FEV_1/FVC*	0.58 (0.13)
Airflow Obstruction; n (%)	
None^	2 (20%)
GOLD I	2 (20%)
GOLD II	4 (40%)
GOLD III	2 (20%)

(*Continued*)

Table 1 (Continued).

Characteristic	N=10 Patients
TLC % Predicted	114.6 (10.3)
RV % Predicted	140.4 (26.7)
RV/TLC	50.3 (9.4)
% Emphysema (−950 HU)	9.5 (13.3)
% Emphysema (range)	0.0%-40.7%
6MWT (meters)	396.9 (54.8)
CAT Total Score	25.4 (4.7)
CAT Phlegm Score	3.8 (0.42)
CAT Cough Score	4.0 (0.67)
SGRQ Total Score	56.2 (8.8)
SGRQ Symptoms Score	75.0 (9.4)
COPD Medications	
LABA and/or LAMA	9 (90.0)
Inhaled Corticosteroid	7 (70.0)

Notes: Data are mean (standard deviation, SD) unless otherwise noted. *Lung function parameters are post-bronchodilator. ^ Two patients enrolled without classically defined COPD (FEV_1/FVC >0.7).

Abbreviations: COPD, chronic obstructive pulmonary disease; CB, chronic bronchitis; LABAs, long-acting beta-agonists; LAMAs, long-acting muscarinic antagonists; GCH, goblet cell hyperplasia; OPEP, positive expiratory pressure; PEF, pulsed electric field; CAT, COPD assessment test; FEV_1, forced expiratory volume in one second; CT, computed tomography; 6MWT, six-minute walk test; CBC, complete blood count; SGRQ, St. George's respiratory questionnaire; CASA-Q, cough and sputum assessment questionnaire; H&E, hematoxylin and eosin; PAS, periodic acid Schiff; FVC, forced vital capacity; TLC, total lung capacity; DLCO, diffusion capacity; GOLD, Global Initiative for Obstructive Lung Disease; SAE, serious adverse event; MCID, minimal clinically important difference.

of 4 points.[15] This outcome was reached in 7 of 10 patients at 3 months, 8 of 10 patients at 6 months, and 7 of 10 patients at 12 months (Figure 4). Mean changes from baseline in total SGRQ score were −14.8, −19.6, and −15.2 at Months 3, 6, and 12, respectively. Similar to the other patient reported outcomes, there was a consistent improvement in the CASA-Q, both cumulatively and in each individual domain (Supplementary Figure 1).

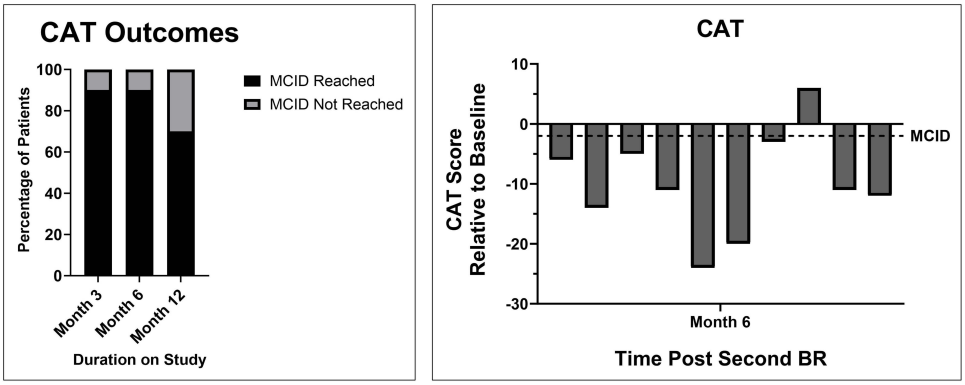

Figure 3 COPD Assessment Test (CAT) Outcomes. The minimally clinically important difference (MCID) for the CAT is a change of 2 points.[14] This change was reached in 9 of 10 patients at 3 months, 9 of 10 patients at 6 months, and 7 of 10 patients at 12 months.

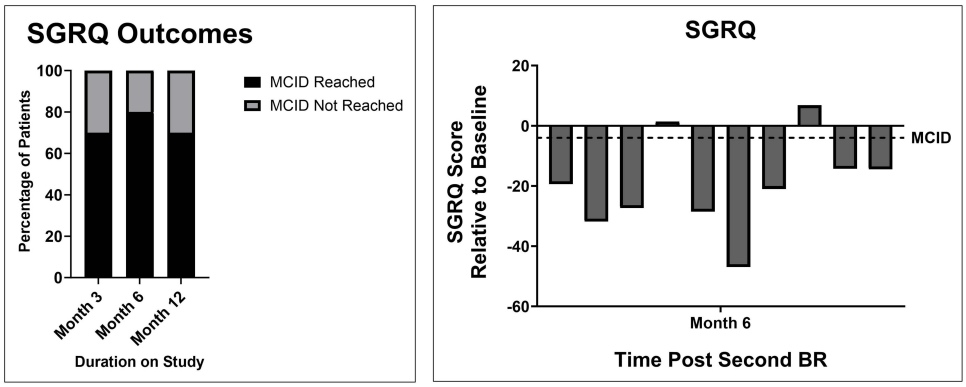

Figure 4 Saint George's Respiratory Questionnaire (SGRQ) Outcomes. The MCID for SGRQ is a change of 4 points.[15] This outcome was reached in 7 of 10 patients at 3 months, 8 of 10 patients at 6 months, and 7 of 10 patients at 12 months.

No clinically meaningful changes were observed in pulmonary function results or 6MWT following treatment. Evaluation of post-treatment changes from the imaging data demonstrated a mean (SD) distal airway volume improvement of 10.7% (35.6) on inspiration scan and 15.8% (100.8) on expiration scan.

Assessment of the mucosal biopsies indicated patients had a mean GCH score of 1.57±0.8 (n=7) prior to treatment (Figure 2). Due to issues with sample integrity, only 4 of the 10 patients had biopsies that were evaluable at both baseline and 3-month follow-up. In these four patients, a 24% reduction (mean (SD) change from 1.81 (0.55) to 1.38 (1.09)) in GCH score was observed at the 3-month follow-up bronchoscopy.

Discussion

We present results from a prospective, three center single arm study of BR in a Canadian cohort of symptomatic CB patients assessing safety and feasibility. In this study, BR appears safe with only 1 SAE deemed possibly related to the device and procedure out of the twenty procedures conducted. Importantly, while the therapeutic impact is, at least in part, a consequence of the electrical energy, no cardiac rhythm aberrancies occurred during any of the procedures.[16] Finally, non-serious adverse events reported were as expected in this patient population undergoing multiple bronchoscopies.[14]

The secondary outcome of clinical utility demonstrated a clinically meaningful improvement in quality of life in this cohort, per CAT and SGRQ scores. Moreover, this was achieved in the overwhelming majority of patients and was maintained through at least 12 months. While similarities exist between this cohort and the previously published one, there are some differences to note. Specifically, there was no enforced restriction on low attenuation area scores for emphysema in this patient cohort. Additionally, patients without airflow obstruction (defined by an FEV_1 to FVC ratio of less than 0.7) were not excluded from this cohort, rather, patients were included as long as they met the inclusion criteria of an FEV_1 between 30% and 80% of the predicted. As noted, while there were no imaging-based exclusions for emphysema in this study, one patient had severe emphysema on imaging with a low attenuation area (LAA) of >40% and one patient had an LAA of ~25%. Interestingly, this latter patient was also the one patient that was most consistent without a symptomatic response. Although the mucosal biopsy data is quite limited by the number of patients with evaluable tissues, those findings are also consistent with previously published data. The overall improvement in distal airway volume on CT may be the result of both an improvement in mucus clearance and a reduction in both mucus production and airway inflammation as a consequence of the BR. Finally, pulmonary function testing remained stable throughout the duration of the study suggesting no airway injury or stenosis resulting from treatment. The primary limitations of this study are the small sample size including limited biopsy data and lack of control group.

Conclusion

This study demonstrates the safety and clinical feasibility of BR using RheOx in this cohort of patients. Only a single SAE was attributed as possibly related to the investigational device and procedure, and there appeared to be meaningful

improvement in clinical utility measured by CAT and SGRQ through 12 months. These results further support available data around the safety and feasibility of BR in chronic bronchitis patients, for whom there remains a significant unmet therapeutic need to relieve symptom burden and improve quality of life. Further study is required to confirm these results.

Data Sharing Statement

Written requests for deidentified participant data will be reviewed and may require data use agreements. Requests should be directed to the corresponding author.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

Dr Simon Martel reports fee to his institution for patient recruited and treated to cover all the hospital charges from IUCPQ. The authors report no other conflicts of interest in this work.

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