On the Potential Role of MRI Biomarkers of COPD to Guide Bronchoscopic Lung Volume Reduction

Colin J. Adams, MD,1,2 Dante P. I. Capaldi, BSc1,2, Robert Di Cesare2, David G. McCormack, MD, FRCPC3, Grace Parraga, PhD2 for the Canadian Respiratory Research Network

Rationale and Objectives: In patients with severe emphysema and poor quality of life, bronchoscopic lung volume reduction (BLVR) may be considered and guided based on lobar emphysema severity. In particular, x-ray computed tomography (CT) emphysema measurements are used to identify the most diseased and the second–most diseased lobes as BLVR targets. Inhaled gas magnetic resonance imaging (MRI) also provides chronic obstructive pulmonary disease (COPD) biomarkers of lobar emphysema and ventilation abnormalities. Our objective was to retrospectively evaluate CT and MRI biomarkers of lobar emphysema and ventilation in patients with COPD eligible for BLVR. We hypothesized that MRI would provide complementary biomarkers of emphysema and ventilation that help determine the most appropriate lung lobar targets for BLVR in patients with COPD.

Materials and Methods: We retrospectively evaluated 22 BLVR-eligible patients from the Thoracic Imaging Network of Canada cohort (diffusing capacity of the lung for carbon monoxide $= 37 \pm 12\%$predicted, forced expiratory volume in 1 second $= 34 \pm 7\%$predicted, total lung capacity $= 131 \pm 17\%$predicted, and residual volume $= 216 \pm 36\%$predicted). Lobar CT emphysema, measured using a relative area of $< -950$ Hounsfield units (RA950) and MRI ventilation defect percent, was independently used to rank lung lobe disease severity.

Results: In 7 of 22 patients, there were different CT and MRI predictions of the most diseased lobe. In some patients, there were large ventilation defects in lobes not targeted by CT, indicative of a poorly ventilated lung. CT and MRI classification of the most diseased and the second–most diseased lobes showed a fair-to-moderate intermethod reliability ($\kappa = 0.40–0.59$).

Conclusions: In this proof-of-concept retrospective analysis, quantitative MRI ventilation and CT emphysema measurements provided different BLVR targets in over 30% of the patients. The presence of large MRI ventilation defects in lobes next to CT-targeted lobes might also change the decision to proceed or to guide BLVR to a different lobar target.

Key Words: Bronchoscopic lung volume reduction; hyperpolarized noble gas; magnetic resonance imaging; computed tomography; chronic obstructive pulmonary disease.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by a chronic airflow limitation associated with airway inflammation due to long-term exposure to inhaled toxins and particles (1). In patients with COPD, emphysematous tissue destruction and narrowing of the small airways contribute to airflow limitation (2), lung hyperinflation, dyspnea, and worsening quality of life (3). Emphysema is inexorably progressive and irreversible, whereas lung hyperinflation also worsens over time and leads to worsening lung compliance, loss of exercise capacity, increased frequency of exacerbations, and a significant decline in quality of life (4). To improve symptoms and quality of life in patients with very severe COPD and extensive emphysema, lung volume reduction techniques were developed to selectively reduce or remove emphysematous tissue (5–7).

The overarching goal of lung volume reduction methods is to improve lung function and to decrease hyperinflation, which together result in improved patient quality of life and functional status (8). Such surgical approaches, however, are associated with significant morbidity and mortality (9).
However, in a specific subgroup of patients with heterogeneous upper lobe predominant emphysema and poor functional status, there were significant benefits (10–12), including modest improvements in quality of life (10,13). Since then, a number of minimally invasive bronchoscopic lung volume reduction (BLVR) approaches have been developed (7,14–20) with the goal of improving outcomes and diminished morbidity and mortality associated with the procedure. Several methods have been pioneered, including coils to collapse large airways (16,18), one-way endobronchial valves to promote passive collapse and deflation over time (14,17,19), and thermal vapor ablation to create an inflammatory response with subsequent scarring and loss of volume (7,15). Collateral ventilation is an important determinant of optimal BLVR outcomes (17), although recent studies showed that BLVR using vapor ablation may be unsuccessful regardless of interlobar or intralobar collateral ventilation (7,21,22). For all of these approaches, typically one or two severely diseased lobes are targeted with the aim of diverting blood flow and ventilation to remaining areas of healthier lung parenchymas (11).

The serendipitous finding that better lung volume resection outcomes were reported in patients with computed tomography (CT) evidence of heterogeneous emphysema (10,11) has motivated the use of imaging biomarkers to help improve outcomes post BLVR. Notably, thoracic x-ray CT has been extensively used to quantify lobar disease severity based on emphysema measurements such as the relative area of the lung <=950 HU (RA950). Inhaled noble gas magnetic resonance imaging (MRI) also provides regional emphysema (23) and lung functional (24) information. In particular, in patients with severe COPD, MRI ventilation defects were found to be spatially related to both small-airway disease and emphysema, as well as bronchiectasis (25–30). Importantly, MRI ventilation defects also correlate with pulmonary function measurements (31) and are uniquely predictive of COPD exacerbations in mild-moderate patients who had not previously experienced exacerbations (26).

To our knowledge, MRI biomarkers have not yet been evaluated in patients eligible for BLVR. We think that this is important because regional lung functional information may help explain why some patients who undergo BLVR do not improve and sometimes worsen following treatment, whereas others experience significant improvements in both quality of life and exercise capacity. We hypothesized that MRI would provide new information that would be inconsistent with CT emphysema stratification of patients for BLVR. In other words, in lung regions not targeted for BLVR because of CT emphysema biomarkers, there would be MRI evidence of significant ventilation defects. In such patients, when ventilation is poor in non-BLVR target lobes, BLVR may not be suitable, because we would predict a poorly functioning lung post BLVR, and poor patient outcomes. Hence, our objective here was to retrospectively compare CT biomarkers of emphysema and MRI biomarkers of ventilation for identifying lobar targets for BLVR in a group of patients with severe COPD eligible for BLVR.

**MATERIALS AND METHODS**

**Study Subjects**

All subjects provided written informed consent to a study protocol approved by a local research ethics board and Health Canada (NCT#02279329) (32); all imaging was performed post bronchodilator and subjects were randomized to magnetic resonance (MR) or CT 30 minutes post salbutamol (1:1 ratio) to minimize bias. Participants were recruited from a tertiary care center between 45 and 80 years of age, with a smoking history of ≥10 pack-years and were classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades (33). A total of 197 patients with COPD were considered from the Thoracic Imaging Network of Canada (TINCan) cohort study (32). Patients were included in this retrospective evaluation based on criteria similar to several recent BLVR trials (7,14–20) as well as the original surgical National Emphysema Treatment Trial (NETT) including (10) forced expiratory volume in 1 second (FEV1) = 20–45% predicted, total lung capacity of >100% predicted, residual volume of >150% predicted, as well as a 6-minute walk test distance of ≥140 m. In total, 25 participants met such criteria and three of these did not have CT evidence of emphysema (34), so the remaining 22 patients were evaluated.

**Pulmonary Function Tests**

All participants performed spirometry according to the European Respiratory Society and the American Thoracic Society guidelines (35,36). Full-body plethysmography (MedGraphics Corporation, St. Paul, MN) was used to measure lung volumes; the diffusing capacity of the lung for carbon monoxide (DLCO) was measured using the attached gas analyzer. The St. George Respiratory Questionnaire was used with permission (37) and participants performed the 6-minute walk test according to the European Respiratory Society and the American Thoracic Society guidelines (38).

**Image Acquisition**

MRJ was performed post bronchodilator, using a 3T Discovery MR750 system (General Electric Health Care, Milwaukee, WI). 1H MRI was performed as previously described (28) at inspiration breath-hold after inhalation of 1.0 L of high-purity, medical-grade nitrogen (N2) from functional residual capacity administered using a 1.0 L Tedlar Bag (Jensen Inert Products, Coral Springs, FL). Hyperpolarized 3He static ventilation imaging was also performed, as previously described (32).

CT was acquired within 30 minutes of MRI using a 64-slice scanner (LightSpeed VCT, General Electric Health Care). To prevent the potential for differences in lung volumes between MRI and CT, the patients were transported to CT via wheelchair and images were acquired at the same lung volume and in the same fashion as 3H MRI but with a
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