CHEST

Original Research

INTERVENTIONAL PULMONOLOGY

Biological Lung Volume Reduction*

A New Bronchoscopic Therapy for Advanced Emphysema

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Background: **Biological lung volume reduction (BLVR) using biological reagents to remodel and shrink damaged regions of lung has previously been accomplished in sheep with experimental pulmonary emphysema. This report summarizes the initial clinical experience including a 3-month follow-up using this technique in humans.**

Methods: **An open-label phase 1 trial designed to evaluate the safety of BLVR in patients with advanced heterogeneous emphysema enrolled six patients. Of these, three patients received unilateral treatment at two pulmonary subsegments (group 1) and three patients received unilateral treatment at four pulmonary subsegments (group 2). The incidence of adverse events and changes in pulmonary function test results, symptoms, and exercise capacity were evaluated.**

Results: **The mean (± SD) age of the six men enrolled in the study was 66 ± 5.7 years (age range, 57 to 73 years). BLVR was well tolerated in both treatment groups and was not associated with any serious complications. All patients were discharged from the hospital on posttreatment day 1. Although the primary purpose of the study was to examine safety, improvements were observed in mean vital capacity (+7.2 ± 9.5%; range, −2% to + 19%), mean residual volume (RV) [−7.8 ± 8.5%; range, + 1% to −22%], mean RV/total lung capacity ratio (−6.6 ± 4.7%; range, −1% to −15%), mean 6-min walk distance (+14.5 ± 18.5%; range, 0 to + 51%), and in mean dyspnea score. On average, group 2 patients experienced greater benefit from BLVR than group 1 patients, suggesting a dose-response pattern.**

Conclusions: **Preliminary results indicate that BLVR can be safe and may produce benefits in appropriately selected patients with advanced heterogeneous emphysema.**

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Key words: biological lung volume reduction; bronchoscopic lung volume reduction; COPD; emphysema; lung volume reduction surgery; pulmonary emphysema

Abbreviations: BLVR = biological lung volume reduction; DLCO = diffusing capacity of the lung for carbon monoxide; LVRS = lung volume reduction surgery; MRC = Medical Research Council; RV = residual volume; 6MWD = 6-min walk distance; TLC = total lung capacity

Some studies[1,2] have indicated that lung volume reduction surgery (LVRS) ameliorates dyspnea, increases exercise capacity, improves lung function, enhances health-related quality-of-life measures, and reduces mortality in selected patients with advanced emphysema. Although beneficial to many emphysema patients, LVRS is associated with an operative mortality rate of 4 to 7%, a morbidity rate of 30 to 50%, and an average hospital stay of 10 to 14 days.[3,4] The development of less invasive and less morbid approaches to lung volume reduction would represent a substantial advance in the treatment of emphysema.[5] Several bronchoscopic procedures designed to reduce lung volume in patients with emphysema are under development. These include one-way valves,[6–10] or bronchial occlusive devices to collapse emphysematous regions of lung[11] and bronchial fenestration with bypass stents[12] to improve expiratory flow. Although some progress has been made using endobronchial valves, published pilot studies[9] have revealed inconsistent change in pulmonary function. It is suggested that the extensive

collateral ventilation present in emphysematous lungs appears to limit the effectiveness of endobronchial valves.[13]

Ingenito and associates[14–16] demonstrated in sheep that the bronchoscopic instillation of biocompatible and biodegradable substances collapses targeted portions of the lung and initiates an inflammatory process leading to the formation of localized scar tissue. The scar shrinks the targeted region of lung and reduces its volume over a period of weeks. This biological lung volume reduction (BLVR) [referred to as *bronchoscopic lung volume reduction* in previous publications[14–16]] is reproducible in experimental animals.[14–16] The phase 1 study summarized in this communication was designed to evaluate the safety of BLVR with a 3-month follow-up in patients with advanced emphysema.

Materials and Methods

Patient Selection Criteria

The National Emphysema Treatment Trial established subgroups of emphysema patients in whom LVRS had the greatest benefit and the least risk. These outcomes are reasonably well defined and quantitated.[2,17] The inclusion/exclusion criteria selected for the present study are similar to those used for LVRS. We reasoned that the use of these criteria would allow us to test BLVR in a subset of patients who had been demonstrated to have an acceptable risk for LVRS and also to facilitate the comparison of outcomes. Key inclusion criteria included the following: (1) age > 18 years; (2) clinical and CT scan diagnosis of advanced heterogeneous emphysema; (3) persistent symptoms despite at least 4 weeks of appropriate stable medical therapy (pulmonary rehabilitation was not required); (4) $FEV_1 < 45\%$ predicted; (5) total lung capacity (TLC) and residual volume (RV) by plethysmography of $> 110\%$ and 150% predicted, respectively; (6) Pa_{O_2} of > 60 mm Hg on ≤ 4 L/min oxygen and Pa_{CO_2} of < 60 mm Hg; (7) pulmonary systolic artery pressure of ≤ 45 mm Hg; (8) 6-min walk distance (6MWD) of ≥ 150 m; and (9) dyspnea (Medical Research Council [MRC] dyspnea score of ≥ 2. Key exclusion criteria included the following: (1) tobacco use within 16 weeks of screening; (2) comorbidities associated with < 2 years of expected survival; (3) general medical conditions associated with a high risk for general anesthesia or bronchoscopy; (4) previous lung transplantation or LVRS; (5) giant bullous emphysema characterized by one or more dominant bullae (size, > 5 cm) with compression of the lung parenchyma; and (6) $FEV_1 < 20\%$ predicted combined with either a diffusing capacity of the lung for carbon monoxide (DLCO) of $< 20\%$ predicted or homogenous emphysema.[17]

Study Design

This open-label, nonrandomized safety study incorporated two groups of patients. Patients in group 1 (three patients) were to receive BLVR at two pulmonary subsegments in one lung. If during a 3-month follow-up no serious adverse events related to BLVR were encountered, the treatment of three additional patients at four pulmonary subsegments in one lung (group 2) could be initiated. Long-term follow-up was planned for a minimum of 2 years. The protocol was approved by the institutional review boards of the participating hospitals. All patients signed informed consent forms at the time of study enrollment and prior to treatment. Changes in medications after BLVR to meet clinical needs were permitted.

The term *dose* was defined as the number of subsegments targeted. Studies in sheep and consideration of human lung anatomy indicated that each pulmonary subsegment represented 2 to 3% of TLC. Consequently, BLVR performed at two subsegments (group 1) was expected to reduce lung volume by only 4 to 6% of TLC and was not anticipated to produce physiologic benefits. Treatment at four subsegments (group 2) had greater potential for a therapeutic impact (lung volume reduction, 8 to 12%). Moreover, we postulate that BLVR at 5 and 10 subsegments would be the equivalent of unilateral and bilateral LVRS, respectively.

The BLVR Procedure

Patients were treated in the operating room under general anesthesia using short-acting IV agents (*eg*, remifentanil and propofol). ECG, BP, arterial oxygen saturation levels, and body temperature were monitored throughout the procedure. The patients were anesthetized, intubated orotracheally, and stabilized using a mechanical ventilator. Arterial blood gas level determinations were obtained from a radial arterial line throughout the procedure to monitor the effects of treatment on gas exchange.

The most diseased pulmonary subsegments in one lung, as assessed by a review of CT scans, were preselected for BLVR treatment. Following the stabilization of the patient receiving mechanical ventilation, a flexible bronchoscope was introduced inside the endotracheal tube. The bronchus leading to the target subsegment was identified, and the bronchoscope was then advanced into wedge position in order to prevent the backflow of BLVR reagents. Wedging was tested by applying suction and observing the collapse of the distal airways.

With the bronchoscope in a wedge position, the BLVR proce-

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