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Original Research

Endobronchial Coils Versus Lung Volume Reduction Surgery or Medical Therapy for Treatment of Advanced Homogenous Emphysema

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Abstract

Rationale: Bronchoscopic lung volume reduction utilizing shape-memory nitinol endobronchial coils (EBC) may be safer and more effective in severely hyperinflated homogeneous emphysema compared to medical therapy or lung volume reduction surgery (LVRS).

Methods: The effect of bilateral EBC in patients with homogeneous emphysema on spirometry, lung volumes and survival was compared to patients with homogeneous emphysema randomized in the National Emphysema Treatment Trial (NETT) to LVRS or medical therapy. NETT participants were selected to match EBC participants in age, baseline spirometry, and gender. Outcomes were compared from baseline, at 6 and 12 months.

Results: There were no significant baseline differences in gender in the EBC, NETT-LVRS or medical treatment patients. At baseline no differences existed between EBC and NETT-LVRS patients in forced expiratory volume in 1 second (FEV_1) or total lung capacity (TLC) %-predicted; residual volume (RV) and diffusing capacity of the lung for carbon monoxide (DL_{CO}) %-predicted were higher in the EBC group compared to NETT-LVRS ($p<0.001$). Compared to the medical treatment group, EBC produced greater improvements in FEV_1 and RV but not TLC at 6 months. FEV_1 and RV in the EBC group remained significantly improved at 12-months compared to the medical treatment group. While all 3 therapies improved quality of life, survival at 12 months with EBC or medical therapy was greater than NETT-LVRS.

Conclusion: EBC may be a potential therapeutic option in patients with severe homogeneous emphysema and hyperinflation who are already receiving optimal medical treatment.

Abbreviations: endobronchial coils, **EBC**; lung volume reduction surgery, **LRVS**; National Emphysema Treatment Trial, **NETT**; forced expiratory volume in 1 second, **FEV_1**; total lung capacity, **TLC**; residual volume, **RV**; diffusing capacity of the lung for carbon monoxide, **DL_{CO}**; St George's Respiratory Questionnaire, **SGRQ**; computed tomography, **CT**; standard deviation, **SD**; analysis of variance, **ANOVA**; forced vital capacity, **FVC**; minimal clinically important difference, **MCID**

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Introduction

Hyperinflation is commonly associated with advanced homogenous emphysema and causes significant morbidity and mortality. Hyperinflation may adversely affect lung and chest wall mechanics and impair respiratory muscle performance.[1,2] Because of these adverse physiological effects, hyperinflation significantly contributes to shortness of breath, impaired quality of life, development of respiratory failure and increased mortality.[3-7] Conversely, hyperinflation may be reduced with bronchodilators, supplemental oxygen and pulmonary rehabilitation.[8-11] The most potent approach to treat hyperinflation is lung volume reduction surgery (LVRS). In hyperinflated emphysematous patients, LVRS has been shown to improve lung and respiratory muscle function, exercise performance, quality of life and in select patients, mortality.[12-14]

LVRS, however, is associated with substantial morbidity and mortality.[13,15] Consequently, the numbers of patients receiving LVRS has steeply declined over the past decade both in the United States and abroad.[16] Minimally invasive bronchoscopy techniques that can reduce lung volume with less morbidity have been recently reported. One of these techniques uses sub-segmental airway insertion of shape-memory nitinol endobronchial coils (EBC) that are effective independent of the presence of collateral ventilation. Several studies have shown that this technique improves quality of life, lung function and 6-minute walk distance in patients with heterogeneous and homogenous emphysema,[17-23] and in a small study also in strictly homogeneous emphysema.[24] Recently, 3 randomized controlled trials enrolled heterogeneous and homogenous emphysema patients, demonstrating a modest exercise improvement following EBC, with substantial improvements in quality of life (St George's Respiratory Questionairre [SGRQ]). In each trial, approximately two-thirds of the participants had homogeneous emphysema.[18,21,22] Homogenous patients are of particular interest since LVRS increases the risk of death in these patients.[15] Lung transplantation is the only option other than medical therapy; the latter, even when optimized, fails to produce dramatic improvements or substantially improve survival in patients with advanced emphysema.[16,25]

We hypothesized that bronchoscopic lung volume reduction utilizing EBC would be more effective than usual medical care in severely hyperinflated emphysema patients, with fewer complications compared to LVRS.

Methods

Patient Population

We evaluated consecutive patients with homogenous emphysema who underwent bilateral EBC in previously reported clinical trials.[17,22,23] EBC treatment was targeted to the most emphysematous regions of the lung. We compared them to another cohort of individuals with homogenous emphysema who had been enrolled into the National Emphysema Treatment Trial (NETT).[13,26] All patients with

homogeneous emphysema were eligible for inclusion and were selected by matching lung function and sex to the EBC group. NETT was a prospective randomized and controlled multicenter clinical trial that compared LVRS to optimal medical therapy on the co-primary endpoints of survival and maximum exercise performance.[26]

Lung Function and Exercise Tolerance

Spirometry was obtained pre and post bronchodilator administration. Only post bronchodilator values are reported. Lung volumes were determined post bronchodilator administration by body plethysmography.[27,28] The 6-minute walk distance (6MWD) test was performed in a well-marked 100-foot corridor by conventional performance standards.[29]

Quality of Life Assessment

The SGRQ was used to measure disease specific indices of quality of life. The SGRQ consists of symptoms, activity and social impact components and a higher score indicates worse quality of life. The instrument was self-administered according to published standards.[30]

Homogenous Emphysema Determination

Three independent readers reviewed the EBC baseline chest computed tomography (CT) scans and qualitatively scored them for the degree of emphysema using the NETT protocol: the lungs were divided into 3 separate regions: upper (apex to aortic arch); mid (aortic arch to inferior pulmonary vein); and lower zones (inferior pulmonary vein to diaphragm).[13,26] A difference in qualitative scores <2 defined homogenous emphysema by the following scoring system:

0% lung destruction = score 0
1%-25% lung destruction = score 1
26%-50% lung destruction = score 2
51%-75% lung destruction = score 3
75%-100% lung destruction = score 4

If a single lung was homogenous the patient was considered to have homogenous emphysema.

Primary Outcomes

Changes in post bronchodilator spirometry, lung volumes and survival in EBC patients at 12 months post procedure were the primary outcomes compared to the NETT medical therapy or NETT-LVRS arms.

Data Analyses

Data is reported as mean ± standard deviation (Mean ± SD) unless otherwise indicated. Data was analyzed by analysis of variance (ANOVA) to determine statistical significance. Least mean squares using ANOVA with factors of treatment and baseline values was used in the final determination of statistical significance. A $p<0.05$ was considered statistically significant. Survival analysis was conducted using a Kaplan-Meier analysis.

Results

Patient Demographics

Data were comprehensively analyzed for 179 patients (85, EBC; 51, NETT-LVRS; 43, medical treatment) as shown in Table 1. NETT-LVRS and medical treatment patients were slightly older compared to EBC patients ($p<0.01$). Baseline lung function was similar in all 3 groups except diffusion capacity was lower in the NETT-LVRS group compared to the EBC or medical treatment groups ($p<0.001$). Baseline 6MWD was highest in the NETT-LVRS group compared to the EBC and medical treatment groups ($p<0.001$) and baseline quality of life was worse in the EBC compared to the NETT-LVRS or medical treatment groups ($p=0.008$).

Table 1. Baseline Characteristics

	EBC n = 85	NETT-LVRS n = 51	Medical Treatment n = 43	*p*
Age, years	61.0 ± 8.1	64.2 ± 4.4	64.0 ± 4.1	<0.01
Male Sex, n (%)	39 (46)	24 (47)	29 (68)	0.06
FVC, % predicted	74.8 ± 17.0	70.5 ± 13.4	72.2 ± 10.8	0.10
FEV_1, % predicted	27.6 ± 7.3	26.8 ± 3.8	27.6 ± 4.3	0.38
FEV_1/FVC, %	30.8 ± 7.8	30.6 ± 5.9	30.5 ± 6.0	0.50
TLC, % predicted	137.9 ± 19.0	135.4 ± 8.9	136.3 ± 9.3	0.34
RV, % predicted	247.3 ± 55.1	234.2 ± 26.9	236.6 ± 28.5	0.09
RV/TLC, %	65.8 ± 8.0	65.1 ± 7.1	62.4 ± 5.2	0.61
DL_{CO}, % predicted	33.4 ± 10.6	26.1 ± 7.2	32.5 ± 10.1	<0.001
6MWD, meters	310.8 ± 96.6	371.4 ± 84.1	342.3 ± 99.9	<0.001
SGRQ, total	60.1 ± 13.7	53.4 ± 14.4	53.3 ± 14.1	0.008

FVC=functional residual capacity; FEV_1=forced expiratory volume in 1 second; TLC=total lung capacity; RV=residual volume; DL_{CO}=diffusion capacity of the lung for carbon dioxide; 6MWD=6-minute walk distance; SGRQ=St George's Respiratory Questionnaire; EBC=lung volume reduction coil with homogeneous emphysema; NETT LVRS=National Emphysema Treatment Trial lung reduction surgery cohort; NETT medical=National Emphysema Treatment Trial medical treatment cohort with homogeneous emphysema

Changes in Lung Function and 6-Minute Walk Distance

Table 2 shows changes in pulmonary function measures in patients at 6 and 12 months post intervention compared to baseline in the EBC, NETT-LVRS and medical treatment groups. As shown, there was no significant difference in changes in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and FEV_1/FVC between groups. There was a trend toward a higher FVC in the EBC group at 12 months (p=0.08).

At 6-months there was a significant decrease in residual volume (RV, p=0.002) and total lung capacity (TLC, p<0.001) in both the EBC and NETT-LVRS groups compared to medical therapy. The magnitude of the decline in RV and TLC was greater in NETT-LVRS than EBC. At 12 months there remained a significant decline in RV (p=0.006) and TLC (p<0.001) compared to baseline in both the EBC and NETT-LVRS groups compared to medical therapy alone.

Following treatment with EBC, the 6MWD improvement was greater in comparison to the NETT-LVRS or medical treatment groups at 6 (p<0.001) and 12 months (p=0.001, Figure 1) .

Changes in Quality of Life

In all 3 groups, SGRQ total and its subcomponent scores of symptoms, activities, and impacts decreased greater than what is considered the minimal clinically important difference (MCID) evidencing an improved quality of life at 12 months compared to baseline (Table 3). Although not statistically significant, the mean reduction in total SGRQ was greatest following EBC at 12 months when compared to the other groups.

Survival

Figure 2 shows a Kaplan-Meir survival curve at 12 months following the 3 interventions. EBC and medical treatment groups both showed an increased survival compared to the NETT-LVRS group at 1 year (p<0.001).

Discussion

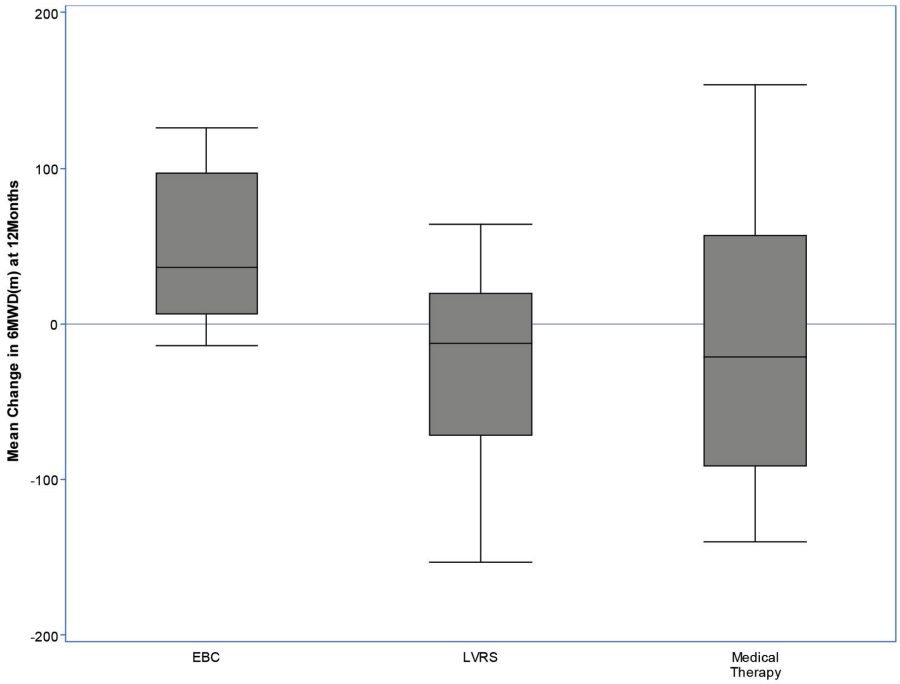
Our results demonstrate that placement of endobronchial coils in patients with advanced homogeneous emphysema reduced residual volume, total lung capacity, and increased 6MWD compared to optimal medical therapy. Additionally, placement

Table 2. Changes in Spirometry and Lung Volumes at 6 and 12 Months Post Intervention Compared to Baseline

	EBC (n = 85)	NETT LVRS (n = 51)	NETT Medical (n = 43)	*p* value
Change from Baseline to 6 Months	n = 77	n = 35	n = 33	
FVC(L)	0.30 (0.20 to 0.39)	0.20 (0.06 to 0.34)	0.01 (-0.14 to 0.15)	0.27
FEV_1 (L)	0.11 (0.07 to 0.14)	0.11 (0.05 to 0.16)	0.01 (-0.05 to 0.07)	0.91
FEV_1/FVC	0.14 (-0.92 to 1.19)	1.36 (-0.20 to 2.92)	0.23 (-1.37 to 1.84)	0.20
RV (L)	-0.58 (-0.74 to -0.42)	-1.04 (-1.28 to -0.80)	0.02 (-0.23 to 0.26)	0.002
TLC (L)	-0.27 (-0.41 to -0.12)	-0.92 (-1.14 to -0.70)	-0.03 (-0.26 to 0.19)	<0.001
RV/TLC (L)	-5.22 (-6.42 to -4.02)	-6.56 (-8.38 to -4.75)	-0.58 (-2.48 to 1.33)	0.22
Change from Baseline to 6 Months	n = 50	n = 28	n = 31	
FVC (L)	0.32 (0.19 to 0.45)	0.12 (-0.05 to 0.30)	0.02 (-0.15 to 0.18)	0.08
FEV_1 (L)	0.11 (0.05 to 0.17)	0.05 (-0.03 to 0.12)	0.01 (-0.07 to 0.08)	0.19
FEV_1/FVC	-0.13 (-1.49 to 1.22)	-0.30 (-2.10 to 1.51)	0.24 (-1.46 to 1.95)	0.89
RV (L)	-0.53 (-0.74 to -0.32)	-1.03 (-1.32 to -0.75)	-0.08 (-0.36 to 0.19)	0.006
TLC (L)	-0.34 (-0.53 to -0.14)	-0.94 (-1.20 to -0.67)	-0.11 (-0.36 to 0.15)	<0.001
RV/TLC (L)	-4.14 (-5.91 to -2.37)	-6.47 (-8.88 to -4.06)	-0.90 (-3.23 to 1.43)	0.12

FVC=functional residual capacity; FEV_1=forced expiratory volume in 1 second; RV=residual volume; TLC=total lung capacity; EBC=lung volume reduction coil with homogeneous emphysema; NETT LVRS=National Emphysema Treatment Trial ung volume reduction surgery cohort; NETT medical=National Emphysema Treatment Trial medical treatment cohort with homogeneous emphysema

Figure 1. Six-Minute Walk Distance



Six-minute walk distance is improved at 6 and 12 months following EBC compared to NETT-LVRS and medical therapy.
6MWD=6-minute walk distance; EBC=endobronchial coils; LVRS=long volume reduction surgery

Table 3. Effect of NETT-LVRS, Medical Treatment and EBC on Quality of Life as Measured by Changes in SGRQ at 12 Months Post Randomization to Therapy

	EBC n = 85	NETT-LVRS n = 51	Medical Treatment n = 43	*p* value
Change in SGRQ Total Score	-7.19 (-10.88 to -3.49)	-5.78 (-10.42 to -1.14)	-5.17 (-9.87 to -0.46)	0.64
Change in SGRQ Symptoms Score	-5.10 (-10.10 to -0.09)	0.03 (-6.29 to 6.36)	-0.80 (-7.21 to 5.61)	0.21
Change in SGRQ Activities Score	-5.73 (-10.48 to -0.99)	-7.95 (-13.87 to -2.04)	-6.09 (-12.09 to -0.09)	0.56
Change in SGRQ Impacts Score	-7.84 (-11.17 to -3.88)	-7.20 (-12.14 to -2.25)	-6.76 (-11.76 to -1.75)	0.84

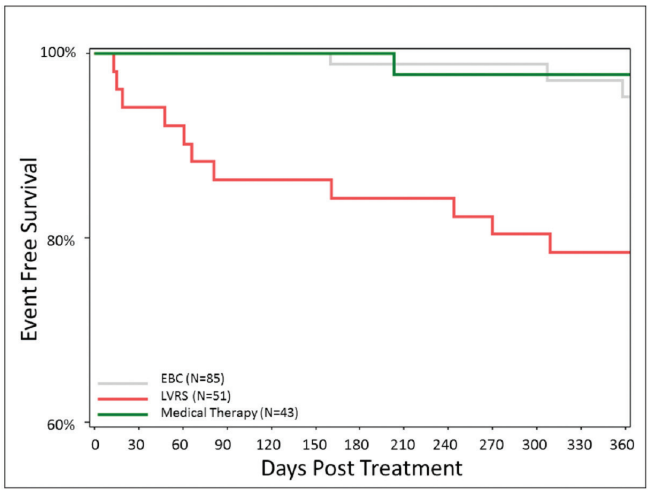
SGRQ=St George's Respiratory Questionnaire; EBC=lung volume reduction coil with homogeneous emphysema; NETT LVRS=National Emphysema Treatment Trial lung volume reduction surgery cohort; NETT medical=National Emphysema Treatment Trial medical treatment cohort with homogeneous emphysema

of endobronchial coils improved 6MWD and survival compared to LVRS. These data suggest that placement of lung coils that reduce end-expiratory lung volume may be a potential therapeutic option in patients with advanced homogeneous emphysema and hyperinflation who are already receiving optimal medical treatment.

Patients with advanced homogeneous emphysema and severe hyperinflation suffer from significantly increased morbidity and mortality. Data from the NETT show that these patients, despite receiving optimal medical treatment while participating in a clinical trial, have a 5-year mortality of 50% and significantly reduced exercise tolerance, 6-minute walk performance, and impaired quality of life.[13-16] Furthermore, LVRS in this patient group produces no significant improvements in lung function, maximum exercise or 6MWD and is associated with increased mortality.[15] Bronchodilators, pulmonary rehabilitation and supplemental oxygen are the mainstays of treatment for this group despite marginal effectiveness. A previous bronchoscopic intervention study investigating the airway bypass approach in homogeneous emphysema patients showed no efficacy 6 months after treatment.[31] Therefore, other than lung transplantation, patients with advanced homogenous emphysema have no effective treatment options.[16,25]

Initial studies examining the impact of endobronchial coils to improve outcomes in severe emphysema have shown benefit in patients with both heterogeneous and homogenous emphysema. Benefits have included improvements in lung function, 6MWD and quality of life with lung coil placement compared to usual care.[17,20,23,24] However, these were non-controlled studies. Shah et al showed substantial improvement in exercise capacity and quality of life at

Figure 2. Kaplan-Meir Survival Curve at 12 months Following the Three Interventions



EBC and NETT medical groups show a comparable and increased survival compared to the NETT LVRS group at one year (p<0.001).
EBC=endobronchial coils; LVRS=long volume reduction surgery

3 months compared to medical treatment with coil placement in a small randomized, controlled study that included both heterogeneous and homogeneous emphysema patients.[22] Two larger randomized, controlled studies comparing EBC to medical therapy were recently completed in which approximately two-thirds of the population in each study had severe homogenous emphysema.[18,21] Overall, coil treatment showed modest improvements in 6MWD, FEV_1 and lung volumes compared to medical therapy.[18,21] Our findings offer further support that EBC may benefit patients with homogeneous emphysema for whom few other options are available.

A recent controlled trial using one-way endobronchial valves demonstrated modest improvements in FEV_1, quality of life and 6MWD in patients with homogeneous disease.[32] In previously published lung reduction trials using bronchoscopic techniques designed to reduce lung volume by atelectasis (endobronchial one-way valves) or fibrosis (lung sclerosant or vapor), patients with very heterogeneous disease had a stronger response than those with less heterogeneous or homogenous disease.[33-35] This is logical since removal of hyperinflated, diseased regions in heterogeneous patients allows more preserved lung tissue to re-expand, while removal of marginally viable lung in homogenous patients may result in expansion of similarly diseased tissue and overall worse functional status. Accordingly, our study shows that patients undergoing EBC had less reduction in residual volume compared to those who underwent LVRS, although 6MWD and survival was improved. Several factors may account for this seemingly disparate outcome between less volume decrease but greater improvements in 6MWD and improved survival. Although LVRS is a more potent lung reduction approach, its increased cardiorespiratory morbidity and mortality outweighs its therapeutic benefit in patients with severe homogeneous emphysema. The post LVRS period is complicated by the need for prolonged acute hospitalization and subacute care secondary to cardiorespiratory complications hallmarked by the ubiquitous presence of air leaks, pneumonia, cardiac arrhythmias, and respiratory failure that may negatively impact 6MWD performance.[13,15] In contrast, homogeneous patients with severe emphysema who undergo EBC suffer from fewer and less severe cardiorespiratory complications allowing patients to improve their functional status post intervention.

In addition, EBC may improve 6MWD by enhancing cardiac performance as a result of decreased hyperinflation. Recent data show the impact of hyperinflation on impairing cardiac function.[36-39] Similar beneficial cardiovascular effects of LVRS have been demonstrated by others.[40-44] Furthermore, lung volume reduction improves chest wall asynchrony and oxygen uptake kinetics.[45,46] These physiologic benefits in aggregate may contribute to the improvement in 6MWD distance as well as survival that we report in the EBC cohort.

Our study is limited because of its retrospective design, and comparison of patients who underwent coil implantation in studies separate from patients who underwent optimal medical treatment and lung volume reduction surgery in the NETT. Although we carefully matched individuals based on their lung function and degree of hyperinflation, there were differences in age, diffusion capacity and gender that we could not control. Additionally, the NETT was conducted from 1998 to 2003. Changes in medical treatment have occurred since NETT compared to the era of the coil implantation studies that have only been recently conducted. Another limitation is that participants did not have standardized care pre and post procedure due to the retrospective nature of the study and difference in available medical therapy. However, a strength of our

study is that we compared data that was prospectively collected in prior well-conducted studies in a patient group that requires novel therapies because of their high morbidity and mortality.

In summary, our data suggest that lung volume reduction via lung coil implantation may be a better alternative than LVRS to improve outcomes in patients with severe hyperinflation and homogeneous emphysema. Future prospective investigation is warranted.

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Declaration of Interest

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