Bronchoscopic lung volume reduction

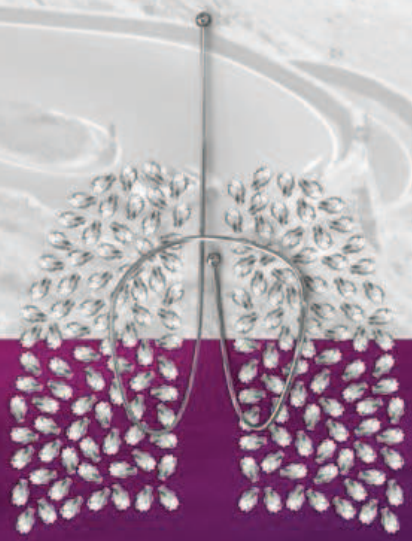
Klooster, Henderika

CHAPTER

7

Bronchoscopic lung volume reduction coil treatment of patients with severe heterogeneous emphysema

Dirk-Jan Slebos
Karin Klooster
Armin Ernst
Felix J. F. Herth
Huib A. M. Kerstjens



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ABSTRACT

Background
The lung volume reduction coil, a new experimental device to achieve lung volume reduction by bronchoscopy in patients with severe emphysema, works in a manner unaffected by collateral airflow. We investigated the safety and efficacy of lung volume reduction coil treatment in patients with heterogeneous emphysema.

Methods
In this prospective cohort pilot study, patients were treated bronchoscopically with nitinol coils under fluoroscopic guidance in either one procedure or two sequential procedures. Follow-up tests included the St. George's Respiratory Questionnaire (SGRQ), pulmonary function testing, and the 6 minute walk test.

Results
Twenty-eight lung volume reduction coil procedures were performed in 16 patients (baseline FEV_1, 28±7.6% of the predicted value). Four patients were treated in one lung, and 12 patients were treated in both lungs. A median of 10 (5-12) coils was placed per lung in 36.5 (20-60) minutes.

Adverse events rated as possibly related to either the device or the procedure, 30 days after treatment were pneumothorax (N=1), pneumonia (N=2), COPD exacerbation (N=6), chest pain (N=4), and mild (<5 mL) hemoptysis (N=21). From 30 days to 6 months, the adverse events that occurred were pneumonia (N=3) and COPD exacerbation (N=14). All events resolved with standard care.

Six months after lung volume reduction coil treatment, there were significant improvements in SGRQ by -14.9±12.1 points (with 11 patients improving by >4 points), in FEV_1 by +14.9±17.0%, in forced vital capacity by + 13.4±12.9%, in residual volume by -11.4±9.0%, and in distance on the 6 minute walk test by + 84.4±73.4 meter (all $P < 0.005$).

Conclusion
Lung volume reduction coil treatment is a promising technique for the treatment of patients with severe heterogeneous emphysema. The treatment is technically feasible and results in significant improvements in pulmonary function, exercise capacity, and quality of life, with an acceptable safety profile.

INTRODUCTION

COPD is an incurable and highly prevalent disease.[1] Patients with advanced emphysema suffer from dyspnea because of decreasing elastic recoil of the lungs, which, along with airway collapse and increased expiratory flow resistance, causes static and dynamic hyperinflation. This hyperinflation is associated with inefficient respiratory muscles, leading to dyspnea and mortality disproportionate to changes in FEV_1.[2,3]

There is currently no cure for emphysema, and the goal of medical treatment is primarily to relieve symptoms and reduce exacerbations using inhaled bronchodilators, anti-inflammatory drugs, proper nutrition, rehabilitation, and supplemental oxygen.[1] Only for a very small subset of patients with COPD are invasive surgical procedures such as lung volume reduction surgery and lung transplantation available.[4] Although the concept of lung volume reduction surgery is excellent, the referral of patients is severely influenced by significant early morbidity.[5] Lung transplantation is even more invasive and, in addition, is limited by donor shortage and unclear survival benefits in COPD.[6]

During the past few years, there has been great interest in bronchoscopic lung volume reduction using different designs of one-way endobronchial valves as an alternative to lung volume reduction surgery.[7,8,9] However, the efficacy of these treatments is limited by both the presence of collateral airflow from adjacent segments, which inhibits the volume reduction of the treated lobe, and the technical difficulty of accurately placing these endobronchial valves in difficult airways anatomy.[9]

At present, efforts are underway to identify responders to one-way endobronchial valve treatment by assessing collateral ventilation.[10] However, the Endobronchial Valve for Emphysema Palliation Trial (VENT) results showed that the majority of patients with heterogeneous emphysema will not benefit from treatment with endobronchial valves,[9] indicating the need for bronchoscopic lung volume reduction treatments that work independently of collateral flow and are less reliant on the very accurate placement of an air sealing device.

To our knowledge, we reported the first study in humans demonstrating the feasibility of bronchoscopic lung volume reduction using a nitinol lung volume reduction coil (LVR-coil) in patients with severe emphysema.[11] In that pilot study, we treated eight patients with severe homogeneous emphysema and three patients with severe heterogeneous emphysema with a median of five coils per lobe. Clinically meaningful improvements were observed only in the heterogeneous patients. In the current study, we further investigate the feasibility, safety, and efficacy of the LVR-coil treatment, specifically in patients with severe heterogeneous emphysema.

METHODS

Study design and population

Patients with heterogeneous emphysema were eligible for this prospective cohort trial. The main inclusion and exclusion criteria are shown in box 1.[12] Heterogeneity was assessed visually by the principal investigator on sagittal reconstructions of a full inspiratory, thin-slice chest CT scan. Emphysema destruction was thereafter digitally assessed by calculating the percentage relative area of destruction below -950 Hounsfield units between the ipsilateral upper and lower lobes of the target lung (Pulmo 2.1; Medis[13,14]). The determination of heterogeneous emphysema was based on identifying disproportionate destruction in the targeted lobe compared with the non-targeted lobe. In this pilot phase, we did not include patients with >75% destruction of the upper lobes. The initial protocol included a 3 month follow-up. During the study this was extended to 6 months, for which the subjects gave additional written informed consent. This study was approved by the University Medical Center of Groningen medical ethics committee (NL26560.042.09).

Box 1. The main inclusion and exclusion criteria.

Inclusion criteria

- FEV_1 <45% of predicted
- Total lung capacity >100% of predicted
- Modified medical research council dyspnea score (mMRC) >1
- Non-smoker for more than eight weeks
- Heterogeneous emphysema

Exclusion criteria

- Change in FEV_1 > 20% post-bronchodilator
- Diffusion capacity < 20% predicted
- Right ventricular pressure >50mmHg
- >3 hospitalizations due to COPD exacerbations in the previous 12 months
- Clinically significant bronchiectasis
- Previous lung surgery, or a giant bulla (> 1/3 of the lung volume)
- Distance on 6 minute walk test <140 meter
- Any use of clopidogrel or coumarines
- Any disease that might compromise survival (such as active lung cancer), or any other disease likely to interfere with completion of study, follow up assessments or that would adversely affect outcomes

Lung volume reduction coils and the procedure

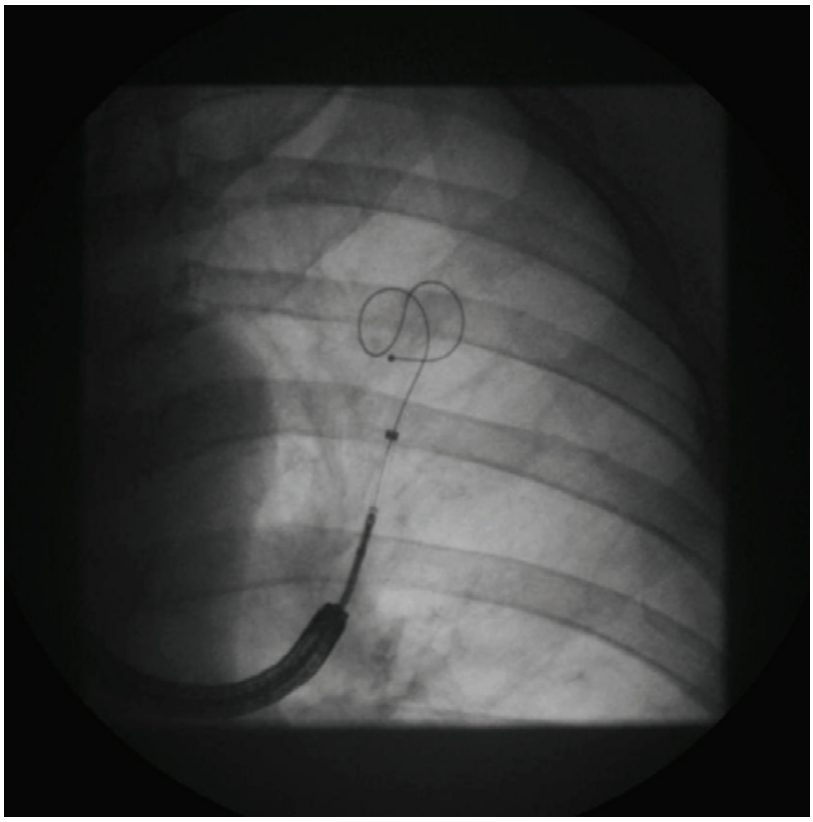
The lung volume reduction coils (RePneu; PneumRx, Inc.) are made from preformed nitinol wire (figure 1), which causes parenchymal compression and is made in a range of lengths (70 to 200 mm) to accommodate airways of different sizes.

Figure 1. Lung volume reduction coil.

The lung volume reduction coil is bronchoscopically delivered straight into (sub) segmental airways and recovers to the predetermined shape upon deployment.

The procedure in this study was performed as described previously,[11] with more coils placed per lobe and by using a standardized segmental treatment algorithm independent of specific CT scan findings (right upper lobe, RB2-RB1-RB3; left upper lobe, LB1/2-LB3-LB4), leaving LB5 untreated because of its proximity to the heart. During bronchoscopy, first the guidewire is advanced into the desired airway under fluoroscopic guidance. A catheter is passed over the guidewire and aligned with the distal tip of the guidewire at 15 mm from the pleura. The length of the airway is measured using radiopaque markers to choose the coil length. The guidewire is then removed, and a straightened coil, preloaded into a cartridge, is pushed forward through the catheter with a biopsy forceps under fluoroscopic guidance. Next, the catheter is removed while the coil is held in place and regains its original shape. Finally, the coil is released from the biopsy forceps. These steps then are repeated for every following coil to be placed. The coil can be removed or repositioned by reversing this implantation process. In this study, the lung volume reduction coil procedure was performed under general anesthesia using a 9.0 mm endotracheal flexible tube and flexible bronchoscope (Olympus BF 180; 2.8 mm working channel, 6.0 mm outer diameter) under fluoroscopy guidance (figure 2). Following recovery from anesthesia, patients stayed one night in the hospital for observation.

Figure 2. Actual deployment of a coil in the LB_1 segment under fluoroscopic guidance.



Follow-up

Safety was assessed by recording all adverse events that occurred. Adverse events were divided into those occurring during the first 30 days after lung volume reduction coil treatment, the period we regarded to be related to the actual procedure, and those occurring during the follow-up period from 1 to 6 months. The primary efficacy variable was change in respiratory related quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ) total score.[15] Additionally, pulmonary function testing (spirometry, body plethysmography, and diffusion capacity) and a 6 minute walk test were performed according to ATS/ERS guidelines.[16,17] Follow-up was performed at 1 and 3 months after the first and second treatment and at 6 months after the final treatment.

Statistics

Results are presented as means ± standard deviation or medians (range) when appropriate. Paired t-tests were used for comparison of results before and after lung volume reduction coil treatment. Microsoft Office Excel 2003 (Microsoft Corporation) and GraphPad Prism (GraphPad Software, Inc) for Windows 4.0 were used for statistical analysis.

RESULTS

Patients

Between April 2009 and March 2010, we recruited 17 and finally treated 16 patients with heterogeneous emphysema (see figure 3 for study flowchart and table 1 for patient demographics and baseline characteristics). The mean emphysema CT scan destruction scores for the right upper lobe were 54.4% (±13.8%) versus 21.2% (±10.4%) for the right lower lobe, and 47.8% (±14.5%) for the left upper lobe versus 18.1% (±9.9%) for the left lower lobe (both differences, $P < 0.0001$).

Twelve patients were treated bilaterally in two sequential procedures, and four patients received lung volume reduction coil treatment of one lung (two patients with only one eligible lung, one patient with underlying coronary artery disease in whom we decided not to treat the second lung, and one patient who improved to such a large degree that we decided not to treat the second lung).

Figure 3. Study flowchart.

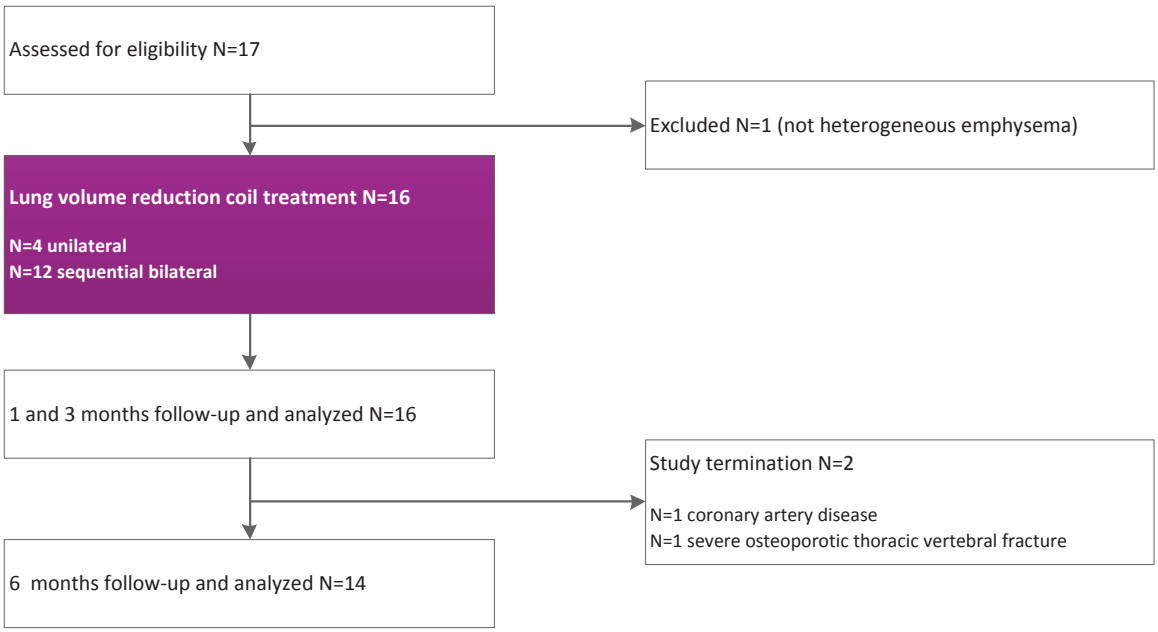


Table 1. Patient demographics and baseline characteristics (N=16).

Characteristic	
Age, years	58±7.3
Female/Male	12/4
Packyears	31±13
BMI, kg/m^2	24.9±3.0
FEV_1, Liter	0.72±0.16
FEV_1, % of predicted value	28.7±7.1
FVC, Liter	2.63±0.83
FVC, % of predicted value	83.1±14.4
RV, Liter	4.42±0.98
RV, % of predicted value	225±43
TLC, Liter	7.32±1.55
TLC, % of predicted value	135±11
Ratio of RV to TLC, %	60.5±6.4
$PaCO_2$, kPa	5.7±0.8
PaO_2, kPa	9.2±1.4
Distance on 6 minute walk test, meter	338±112
mMRC, points	2.8±0.7
SGRQ, points	64±9
BODE index	5.7±1.6
Previous pulmonary rehabilitation	13
Use of home oxygen	4
Medication use	
short acting $beta_2$- agonists	11
long acting $beta_2$- agonists	14
ipratropium	7
tiotropium	13
inhaled corticosteroids	15
acetylcysteine	6
theophylline	2
maintenance prednisolone	6
maintenance antibiotics	5

Data are presented as mean ± standard deviation or absolute numbers.

Lung volume reduction coil procedure

In 28 procedures, 260 coils; median 10 coils (range, 5-12) per procedure were placed. A median time of 36.5 minutes (range, 20-60 minutes) per lung was recorded. No peri-procedural technical events occurred, and all coils could be placed as planned. Follow-up chest radiographs made on day 1, and on 1, 3, and 6 months post procedure (see figure 4 for an example) showed no migration of coils. In four patients, a partial atelectasis due to the coils could be observed on the follow-up radiographs. Of the 260 coils placed in this study, none had to be replaced or removed (see table 2 for all procedural results[18]).

Figure 4. Thoracic radiograph showing the coils in situ in all segments of both upper lobes.

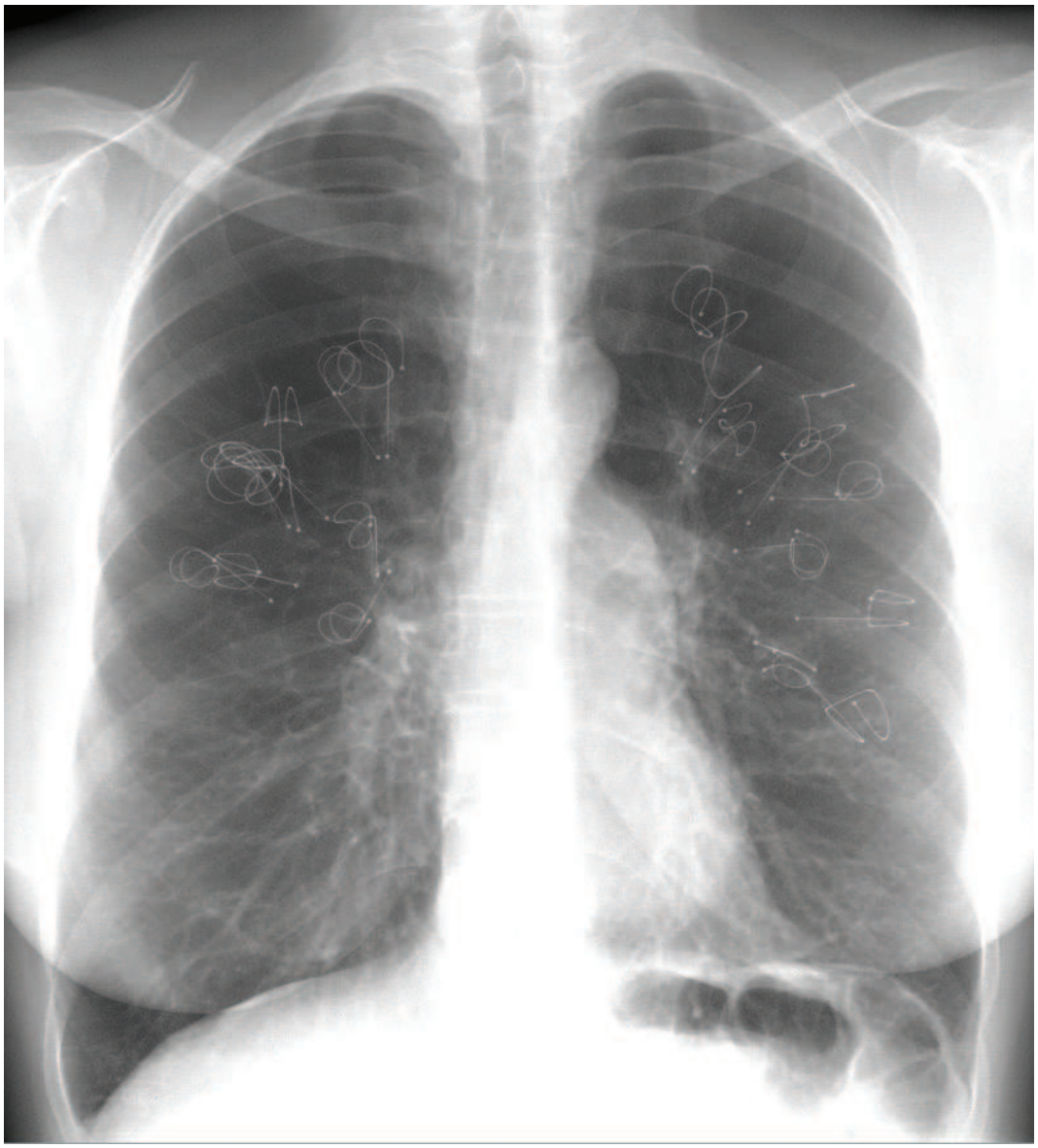


Table 2. Procedural results.

	Number
Lung volume reduction coil procedures, number	28
Unilateral coil procedure RUL/LUL, number of patients	2/2
Bilateral coil, number of patients	12
Procedure time, minute (median, range)	36.5 (20-60)
Total coils placed, number	260
Coils placed per subject, number (median, range)	10 (5-12)
Coils placed per segment, number	
RB_1 (right-apical)	38
RB_2 (right-posterior)	37
RB_3 (right-anterior)	59
$LB_{1/2}$ (left-apicoposterior)	54
LB_3 (left-anterior)	63
LB_4 (left-superior lingular)	9
Coil lengths used, number of coils	
85mm	1
100mm	170
125mm	86
150mm	3

Procedural results are given as absolute numbers and median (range) where indicated. LUL: left upper lobe; RUL: right upper lobe.

Safety

All patients received general anesthesia, uneventfully. In addition, no adverse events during the bronchoscopy or actual coil placements were observed. In 28 procedures, one (< 5%) pneumothorax occurred 1 hour after the bronchoscopy and resolved quickly with a chest tube in 1 day. In 12 patients, mild hemoptysis occurred in 21 procedures (75%) during the first days but resolved spontaneously in all cases. In four cases, transient chest pain occurred, also quickly resolving within a few days after the procedure. At 1 to 6 months follow-up, 16 patients experienced a total of 14 COPD exacerbations, ranging from zero (N=4 patients) to three (N=1 patient) after 28 procedures. In this study, no life-threatening events occurred, and all adverse events could be managed with standard care. All adverse events are listed in table 3a and 3b.

Table 3a. Adverse events.

	number
Any course of prednisolone or antibiotics	
Treatment to 1 month of follow up	8
1 month to 6 months follow up after treatment	17
Respiratory adverse events from 1st and 2nd treatment to 1 month of follow up	
COPD exacerbation	6
Pneumonia	2
Pneumothorax	1
Slight hemoptysis <5 ml	21
Chestpain	4
H1N1 influenza	2
Cough	2
Respiratory adverse events from 1 to 6 months of follow up after completed treatment	
COPD exacerbation	14
Pneumonia	3
Pneumothorax	0
Slight hemoptysis <5 ml	0
Chestpain	2
H1N1 influenza	1
Cough	2
Pulmonary embolism (non treated lung)	1

Adverse events were scored for all 28 procedures performed in 16 patients.

Table 3b. Adverse events.

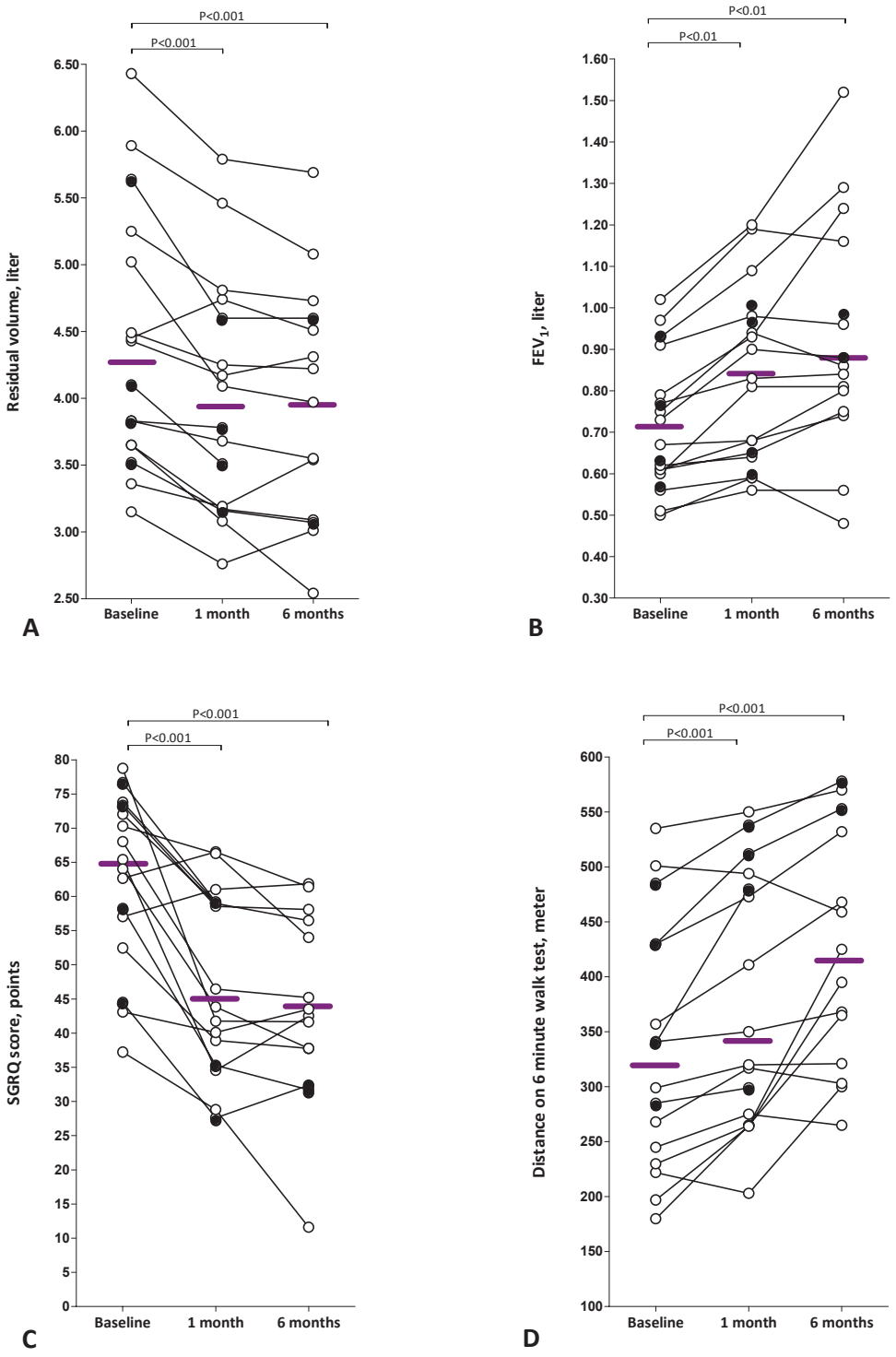
	number
Adverse events related to anaesthesia	
Paroxysmal atrial fibrillation	1
Phlebitis	1
Headache	2
Hoarseness	3
Bronchospasm	1
Adverse events, other causes	
Hypertension	1
Consolidation around LVR-coil	1
Nasal congestion	3
Tonsillar angina	1
Diarrhea	3
Oral candidiasis	3
Urinary tract infection	2
Traumatic rib contusion	1
Osteoporotic thoracic vertebral fracture	1
Gout	1
Wrist fracture	1
Azathioprine induced thrombopenia	1
Anemia	**1**

Adverse events were scored for all 28 procedures performed in 16 patients.

Efficacy

Compared with baseline, after 6 months, lung volume reduction coil treatment resulted overall in a significant improvement in SGRQ by 14.9±12.1 points, P <0.005), in FEV_1 by +14.9±17.0%, in forced vital capacity by +13.4±12.9%, in residual volume by -11.4±9.0%, and in distance on 6 minute walk test by +84.4±73.4 meter. Bilateral treatment further improved the initial single lung 1 month results. The initial responses observed in the pulmonary functions tests, distance on 6 minute walk test, and SGRQ, were sustained throughout the 6 month follow-up period (figure 5, table 4). More than 50% of the patients responded to above the minimal clinical important difference for FEV_1,[19] distance on 6 minute walk test,[20-22] and SGRQ[23] (table 5).

Figure 5. Individual results at baseline, 1 month after the first coil treatment, and 6 months after the last coil treatment.



Individual results at baseline, 1 month after the first coil treatment, and 6 months after the last coil treatment for patients who were treated bilaterally (○) and unilaterally (●). **A**. residual volume **B**. FEV_1 **C**. SGRQ total score **D**. distance on 6 minute walk test. The solid pink colored lines indicate the median values.

Table 4. Lung volume reduction coil treatment efficacy data.

	1 month of follow up post 1st treatment	1 month of follow up post 2nd treatment	3 months post 2nd treatment	6 months post 2nd treatment	6 months of follow up overall post treatments
	N=16	N=12	N=12	N=12	N=14
FVC, %	+11.5±13.6 (P=0.005)	+17.0±14.9 (P0.002)	+10.7±11.9 (P=0.010)	+13.3±13.2 (P=0.007)	+13.4±12.9 (P=0.002)
FEV_1, %	+10.3±13.1 (P=0.009)	+22.6±21.7 (P=0.004)	+19.9±20.0 (P=0.005)	+17.3±19.4 (P=0.010)	+14.9±17 (P=0.004)
RV, %	-9.5±6.5 (P<0.001)	-12.4±9.0 (P<0.001)	-11.1±9.9 (P=0.003)	-10.6±9.59 (P=0.004)	-11.4±9.0 (P<0.001)
Ratio of RV to TLC, %	-6.7±4.8 (P<0.001)	-8.2±7.1 (P=0.002)	-6.6±6.7 (P=0.006)	-8.1±5.2 (P<0.001)	-8.0±5.5 (P<0.001)
6MWD, meters	+35.4±30.6 (P<0.001)	+69.8±64.2 (P=0.003)	+62.2±76.6 (P=0.017)	+80.5±78.8 (P=0.005)	+84.4±73.4 (P<0.001)
6MWD, %	+12.6±13.8 (P=0.003)	+29.8±30.4 (P=0.006)	+27.1±36.6 (P=0.026)	+34.4±39.2 (P=0.011)	+32.9±36.3 (P=0.005)
SGRQ, points	-14.2±11.6 (P<0.001)	-12.2±13.5 (P=0.009)	-12.6±10.8 (P=0.002)	-15.8±12.2 (P=0.002)	-14.9±12.1 (P<0.001)

Data are presented as mean change from baseline ± standard deviation. FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second, RV: residual volume; RV/TLC: ratio of residual volume to total lung capacity. 6MWD: distance on 6 minute walk test; SGRQ: St. George respiratory questionnaire.

Table 5. Responder rate at 6 month after lung volume reduction coil treatment using minimal clinically important difference.

	MCID	Responders	
Forced expiratory volume in 1 second	≥12%[19]	64%	N=9 of 14
Residual volume	≥10%	64%	N=9 of 14
Distance on 6 minute walk test	≥48 meter[20]	64%	N=9 of 14
Distance on 6 minute walk test	≥25 meter[21,22]	86%	N=12 of 14
St. George's respiratory questionnaire	≥4 points[23]	79%	N=11 of 14*

Responder rate given as the number of patients responding per total number of patients treated. MCID=minimal clinically important difference. * 11 of 14 patients improved by >14 points on the St. George's respiratory questionnaire.

DISCUSSION

For patients with advanced stage emphysema, there is a great need for medical treatments that can significantly improve quality of life, without inducing significant morbidity and mortality, and that are potentially available for the majority of patients. In this study, we showed the feasibility, safety, and efficacy of a new bronchoscopic lung volume reduction therapy by using segmentally inserted nitinol coils in patients with severe COPD, characterized by heterogeneous emphysema. From the first safety and feasibility report on the lung volume reduction coil treatment in 11 patients, using only three to six coils per lobe, we learned that patients with heterogeneous emphysema might benefit more than those with homogeneous emphysema.[11]

Therefore, in the current study, we report on patients number 12 to 27, who were treated using this technique with the following refinements: The lung volume reduction coil treatment was optimized by increasing the number of coils per lobe, a second generation coil was used, and the study focused entirely on patients with upper-lobe predominant heterogeneous emphysema. Heterogeneity was determined by a combination of subjective and objective assessments. First, the investigator assessed the sagittal reconstruction of the thin-slice CT scan to determine if there were focal regions of relatively high damage. Then, for cases that appeared to be heterogeneous, quantitative densitometry was used to determine the relative area of destruction (% of volume <-950 Hounsfield units) for both upper and lower lobes of the target lung. Besides lung tissue density quantification, the main role of the densitometry was to place an upper limit on tissue destruction in the treated lobe.

The uncontrolled, open-label design of this study can induce important placebo effects; however, we believe that significant improvements larger than the minimal clinically important difference for FEV_1, residual volume, and forced vital capacity, as well as for the distance on 6 minute walk test,[20-22] are not likely to be attributed to a placebo effect in these severely physically disabled patients. In two large (N=91 and N=98), uncontrolled, lung volume reduction device trials [24,25] in patients with severe upper lobe emphysema, no significant changes were observed in any pulmonary function test or in distance on 6 minute walk test despite bronchoscopic treatment.

In open-label, semi-invasive cohort studies like ours, patient reported outcomes such as the SGRQ can show marked placebo effects, and conclusions should be drawn with some caution. It is known from earlier uncontrolled trials,[8,24-26] for instance, that even without improvements in pulmonary function tests such as FEV_1, forced vital capacity, and residual volume, or exercise testing, the SGRQ improved significantly by more than the minimal clinically important difference[23] after bronchoscopic lung volume reduction. However, in our trial, the improvement was very large (mean improvement of 14.9 points compared with the SGRQ minimal clinically important difference of 4 points). Additionally, we found a close correlation between improvement in residual volume and improvement in SGRQ (eight of the nine patients with a clinically important difference in residual volume of greater than 10% also improved by more than 14 points on the SGRQ). A similarly close correlation was

also reported in a study with intrabronchial valves, in which the improvement in quality of life was associated with procedural efficacy as determined by loss of residual volume on a chest CT scan.[24]

Despite the fact that the lung volume reduction coil treatment was significantly enhanced from a median of five coils in our earlier first-in-human pilot study[11] to a median of 10 coils per lobe in this study, only one pneumothorax (<5%) was experienced, requiring, 48 hours of chest drainage, in 28 procedures using 260 coils. This rate is comparable to that in other bronchoscopic procedures with lung volume reduction devices.[7,24,27] Other adverse events observed that can be related to the actual lung volume reduction coil treatment were transient chest pain, possibly due to pleural traction of the coils, and very mild, transient hemoptysis. In the first month after lung volume reduction coil treatment we observed a relatively high number of exacerbations, related either to the bronchoscopy or to the actual placement of the coils. From previous bronchoscopic intervention trials, it is known that bronchoscopies by themselves induce COPD exacerbations.[28] But it is clear that placing 10 coils in the (sub-) segmental airways of one lobe can cause local airway mucosal damage, local edema, and bronchoconstriction, which may lead to a respiratory event. All events resolved with regular medical care, and no noninvasive ventilatory support or intensive care units admissions were required. After the first month, the frequency of exacerbations returned toward baseline levels.

We performed bilateral lung volume reduction coil treatments as sequential procedures for safety reasons. Early bronchoscopic lung volume reduction trials using one-way valves for total bilateral lobar occlusion reported a high rate of pneumothoraces when these bilateral treatments were performed in a single procedure.[29,30] On the other hand, in the bronchoscopic airway bypass procedure, in which up to 12 trans-bronchial stents were placed in both lungs in a single procedure, the pneumothorax rate remained very low.[28] One could argue that the LVR-coil procedure, in which total lobes are not occluded but only compressed, might be performed bilaterally in a single procedure, thereby significantly reducing the potential risks and costs of repeated bronchoscopy and anesthesia.[31]

Normally functioning lungs are elastic, efficiently expanding, and recoiling to drive air freely through the bronchi to the alveoli and back as the patient inhales and exhales. In the emphysematous lung, tissue is damaged and loses its elasticity.[32] The clinical and pulmonary function benefits seen after lung volume reduction coil treatment might be attributable to volume reduction, similar to the effects seen with lung volume reduction surgery,[33] by compressing diseased lung parenchyma due to the physical elastic properties of the nitinol wire of which the coils are made, and the improved mechanical properties of the remaining tissue that now expands following this compression.[34,35] To elicit these effects, the coils require some minimal amount of lung tissue to compress. Nitinol combines strength and memory shape properties with great elasticity, thereby improving tissue strength and elastic recoil, potentially further reducing the dynamic hyperinflation that occurs easily in these patients.[34,35]

There are currently a number of bronchoscopic lung volume reduction treatments for emphysema under clinical investigation. The available endobronchial one-way valves, designed for segmental and lobar airway closure, only work when there is no, or only very limited, collateral ventilation.[9,24,36] Although these devices work well in patients without collateral ventilation, the low responder rate of these treatments in randomly selected heterogeneous patients clearly shows the need for an intervention that works independently of collateral flow, which is significant in a large proportion of patients with severe emphysema.[36,37] Although the current study reports the results on a small sample, we have already observed a very encouraging responder rate. However, because this was an open-label cohort pilot study, one of the next steps should be to confirm the results in a larger randomized controlled trial, using a more specific definition of heterogeneity as an inclusion criterion. Furthermore, we think that future studies on lung volume reduction coil treatment are warranted in a wider range of emphysema phenotypes such as homogeneous disease.

CONCLUSION

Lung volume reduction coil treatment is a promising novel bronchoscopic technique for the treatment of patients with severe heterogeneous emphysema. The lung volume reduction coil treatment works independently of collateral flow and showed a high responder rate in this early phase clinical trial. The lung volume reduction coil procedure is technically feasible and results in significant improvements in pulmonary function, exercise capacity, and quality of life, with an acceptable safety profile.

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