Bronchoscopic lung volume reduction

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CHAPTER

8

Lung volume reduction coil treatment for patients with severe emphysema: a European multicenter trial

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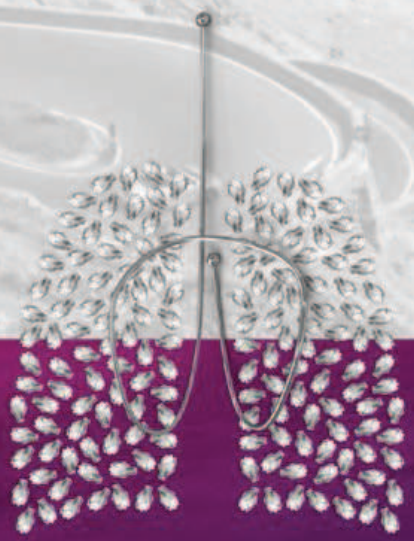

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Key messages

What is the key question?
Is lung volume reduction coil treatment feasible and does it sustainably improve quality of life and clinical outcomes in a broad group of patients with severe emphysema treated in a multicenter setting?

What is the bottom line?
Bronchoscopic lung volume reduction coil treatment is associated with a good safety profile and significantly improves quality of life, exercise capacity and pulmonary function in abroad group of patients with severe emphysema, with sustained results at 1 year.

Why read on?
Further post hoc analysis of CT scan heterogeneity showed significant responses in both heterogeneous and homogeneous emphysema, suggesting that lung volume reduction coil treatment may benefit patients with both heterogeneous and homogeneous emphysema disease distribution.

ABSTRACT

Background
The lung volume reduction coil is a minimally invasive bronchoscopic nitinol device designed to reduce hyperinflation and improve elastic recoil in severe emphysema. We investigated the feasibility, safety and efficacy of lung volume reduction coil treatment in a prospective multicenter cohort trial in patients with severe emphysema.

Methods
Patients were treated in 11 centers. Safety was evaluated by recording all adverse events, efficacy by the St. George's Respiratory Questionnaire (SGRQ) as primary endpoint, and pulmonary function testing, modified Medical Research Council dyspnea score (mMRC) and distance on the 6 minute walk test up to 12 months after the final treatment.

Results
Sixty patients (60.9±7.5 years, forced expiratory volume in 1 second (FEV_1) 30.2±6.3% predicted) were bronchoscopically treated with coils (55 bilateral, 5 unilateral), with a median of 10 (range 5–15) coils per lobe.

Within 30 days post lung volume reduction coil treatment, 7 COPD exacerbations (6%), 6 pneumonias (5%), 4 pneumothoraces (4%) and 1 hemoptysis (1%) occurred as serious adverse events.

At 6 and 12 months, respectively, change in SGRQ was −12.1±12.9 points and −11.1±13.3 points, change in distance on 6 minute walk test was +29.7±74.1 meter and +51.4±76 meter, change in FEV_1 was +0.11±0.20 Liter and +0.11±0.30 Liter, and change in residual volume was −0.65±0.90 Liter and −0.71±0.81 Liter (all $P<0.01$).

Post-hoc analyses showed significant improvements in SGRQ, distance on 6 minute walk test and residual volume in patients with both heterogeneous and homogeneous emphysema.

Conclusion
Lung volume reduction coil treatment results in significant clinical improvements in patients with severe emphysema, with a good safety profile and sustained results for up to 1 year.

INTRODUCTION

For patients with advanced chronic obstructive pulmonary disease (COPD) who, despite optimal medical management still have severe dyspnea, bronchoscopic lung volume reduction could be a beneficial treatment option.[1,2] Although lung volume reduction surgery and lung transplantation are still valid treatment modalities for patients with COPD, the use of these interventions is very limited because of strict patient selection criteria, significant morbidity and donor shortage.[3–5]

To date, bronchoscopic lung volume reduction using one-way endobronchial valves has been the most extensively investigated technique in this field.[6–8] However, successful clinical outcomes from endobronchial valve treatment can only be achieved in patients with no interlobar collateral ventilation and when the one-way valves are placed to entirely block all the airways into the target lobe, which can be technically difficult due to local anatomy and in the absence of significant experience with these devices.[6–8] It is estimated that only about 33% of patients with severe emphysema have no collateral ventilation between the target and adjacent lobe and can thus potentially be treated using one-way valves.[1] This clearly shows the need for alternative bronchoscopic treatments that work independently of the presence of collateral ventilation.

In 2010 we reported the first human trial using bronchoscopically delivered nitinol lung volume reduction coils.[9] Up to six shape-memory coils per lung were placed in patients with severe emphysema, resulting in moderate effects only in the patients with heterogeneous emphysema but without any serious adverse events. After that first trial we improved the lung volume reduction coil treatment to target the most diseased areas of the lung with approximately 10 coils placed per lobe, in order to maximize re-tensioning of the airway network. The results using this approach in 16 patients with upper lobe predominant heterogeneous emphysema have previously been published, showing feasibility and safety and also demonstrating statistically and clinically significant improvements in pulmonary function, exercise capacity and quality of life.[10] Surprisingly, even in this early pilot phase, two-thirds of the patients treated responded beyond the minimal clinically important differences for forced expiratory volume in 1 second (FEV_1),[11] residual volume (RV),[12] distance on 6 minute walk test (6MWD)[13] and St. George's Respiratory Questionnaire (SGRQ).[14]

Following the successful early experiences in these two pilot trials, the current study allowed further investigation into the feasibility, safety and efficacy of lung volume reduction coil treatment in a multicenter setting in a larger group of patients.

METHODS

This prospective open-label multicenter feasibility study was conducted in 11 hospitals in France, Germany and the Netherlands and was approved by the ethics committee at each site. The first patient was enrolled in December 2009 and the final patient in October 2011. The initial protocol proposed a follow-up period of 6 months following initial treatment. However, because the Dutch and French ethics committees required a 12 month follow-up period, the protocol was modified to require a 12 month follow-up for patients in the Netherlands and France, while maintaining the original 6 month follow-up period for patients in Germany. This paper reports on all patients in the study at both exit points.

Patients

Patients with COPD with upper or lower lobe predominant bilateral heterogeneous emphysema on chest CT scan as judged by the treating physician were considered for inclusion. All patients were intended to be treated bilaterally, in accordance with the protocol assessment schedule. The study inclusion and exclusion criteria are presented in box 1.

Box 1. Study inclusion and exclusion criteria.

Main inclusion criteria

- >35 years of age
- CT scan indicates bilateral heterogeneous emphysema
- Post-bronchodilator FEV_1 <45% of predicted
- Total lung capacity >100% of predicted
- Residual volume >175% of predicted
- mMRC >2 (0–4)
- Stopped smoking for >8 weeks prior to entering the study

Main exclusion criteria

- Change in FEV_1 >20% post-bronchodilator
- Carbon monoxide diffusing capacity <20% of predicted
- History of recurrent clinically significant respiratory infection
- Pulmonary hypertension: right ventricular pressure >50 mmHg
- Inability to walk >140 meter in 6 minutes
- Previous lung volume reduction surgery, lung transplant or lobectomy
- Clinically significant bronchiectasis
- Giant bullae more than one-third lung volume
- Severe destructed homogeneous emphysema by CT scan
- Patient on antiplatelet agent or anticoagulant therapy or has not been weaned off prior to procedure

Lung volume reduction coil treatment

Lung volume reduction coil treatment was performed as previously described.[10] Briefly, the RePneu lung volume reduction coil (PneumRx, USA) (figure 1) is an implantable device composed of preformed nitinol wire which is straightened for delivery via a therapeutic flexible bronchoscope into sub-segmental airways using a special delivery catheter, cartridge and loading forceps. Once in place, it is released and recovers to a non-straight predetermined shape upon deployment. Seven sizes of coil were available (70, 85, 100, 125, 150, 175 and 200 mm). All procedures were performed under general anesthesia and the deployment of the coil was visualized under fluoroscopy. The coils were deployed with the objective of achieving equal sub-segmental distribution throughout one target lobe. The contralateral procedure was performed at least 1 month after the first procedure.

Figure 1. Fully deployed nitinol lung volume reduction coils (150, 125 and 100 mm).

Assessments and follow-up

Screening assessments included medical history, physical examination, dyspnea assessment by the modified Medical Research Council dyspnea scale (mMRC), quality of life assessment by the SGRQ,[15] echocardiogram, pre- and post-bronchodilator spirometry, lung volume measurements by body plethysmography,[16] 6 minute walk test,[17] chest X-ray and a thoracic CT scan. The patient was kept at least overnight after the procedure. A 1 month follow-up evaluation was performed, after which the second procedure was scheduled. Patients were then followed at 1, 3, 6 and 12 months (the latter only in France and The Netherlands).

Primary & secondary endpoints and Safety objectives

The primary efficacy endpoint was the improvement in SGRQ total score from baseline compared with the score at 6 months. The secondary efficacy endpoints were the comparison between baseline and 6 months for forced vital capacity (FVC), FEV_1, residual volume, ratio of residual volume to total lung capacity (RV/TLC), improvement in distance on 6 minute walk test and mMRC score. The responder rate at 6 months was calculated using the minimal clinically important difference defined for FEV_1,[11] RV,[12] 6MWD[13] and SGRQ.[14] The safety objectives were to identify the number and type of device-related and procedure related adverse events related to the use of the LVR-coil.

Post-hoc CT scan analyses

Since inclusion in this trial was based on the treating physicians' visual chest CT judgment, a post-hoc analysis was performed on these CT scans to analyze the relationships between the response to lung volume reduction coil treatment at 12 months follow-up and the level of heterogeneity assessed by a blinded qualitative visual 4-point tissue destruction score scale (0–25%, 26–50%, 51–75%, >75% visible tissue destruction), as well as by calculating the percentage area of destruction below −950 Hounsfield units between the upper and lower lobes of both lungs. Quantitative CT analyses were blinded and performed with CIRRUS Lung 13.10 (Diagnostic Image Analysis Group Nijmegen, The Netherlands; Fraunhofer MEVIS, Bremen, Germany). The lungs and lobes were automatically segmented and visually inspected. Emphysema was quantified per lobe as an emphysema score: the percentage of voxels below −950 Hounsfield units.[18] For the visual assessment, a patient was classified as heterogeneous if there was a difference of more than 1 point between ipsilateral lobes on both sides. For the computerized assessment, a patient was classified as heterogeneous when the difference for both lungs in the lung tissue destruction score was >25% at −950 Hounsfield units between ipsilateral upper and lower lobes.

Statistics

This trial was powered on the statistical significant difference in expected SGRQ total score between baseline and the 6 month follow-up time point using an $\alpha<0.05$ with a power of 0.90, taking a patient loss to follow-up of 10% into account.[10]

Data are presented as mean ± standard deviation, except for the presentation of the five unilateral cases and descriptive statistics on the detailed procedural results (table 2) where data are expressed as median (minimum−maximum) or mean ± standard deviation when appropriate. The statistical significance of changes from baseline was assessed by the paired student t-test. A linear regression analysis was performed to associate outcome at 6 months for changes in SGRQ and distance on 6 minute walk test, using as baseline regressors residual volume % of predicted value, ratio of residual volume to total lung capacity, FEV_1 % of predicted value, forced vital capacity, age, carbon monoxide lung transfer factor and emphysema type (homogeneous or heterogeneous disease). The models were simple linear with no interactions or terms higher than first order included; $P<0.05$ was considered statistically significant. SAS version 9.3 was used for all analyses. All data in this trial were independently monitored by a contract research organization.

RESULTS

Patients and procedures

Sixty patients were enrolled between December 2009 and October 2011 and their baseline demographics are shown in table 1. A total of 115 procedures were performed (5 patients had unilateral treatment, figure 2; study flow chart) in which a total of 1125 coils were placed. A median of 10 coils (range 5–15) was placed per lobe (table 2).

Table 1. Patient demographics and baseline characteristics (N=60).

Characteristics	Outcome
Female/Male	33/27
Age, years	60.9±7.5
Pack-years	39.5±18.2
BMI, kg/m²	25±4
FEV_1, Liter	0.83±0.25
FEV_1, % of predicted value	30±6
FVC, Liter	2.49±0.78
FVC, % of predicted value	74±17
Ratio of FEV_1 to FVC, %	34±7
RV, Liter	5.29±1.32
RV, % of predicted value	249±53
Ratio of RV to TLC, %	66±8
Distance on 6 minute walk test, meter	316±102
SGRQ, points	62±14
Supplemental Oxygen, N (%)	35 (58%)
mMRC, points	3.0±0.75

Data are shown as mean ± standard deviation. BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; mMRC, modified Medical Research Council dyspnea score; RV, residual volume; TLC, total lung capacity; SGRQ, St George's Respiratory Questionnaire total score.

Figure 2. Study flow chart.

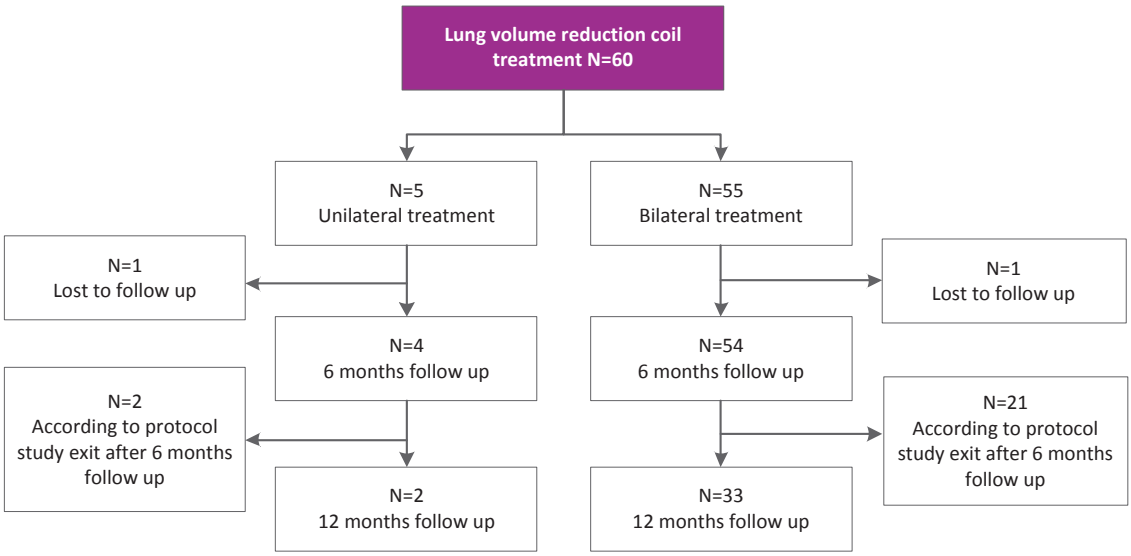

Table 2. Bronchoscopic lung volume reduction coil procedure results.

	Outcome
Number of procedures	115
Procedure time, minutes	
Mean	49.9±23.2
Median	45.0 (20-135)
Post-procedure hospital stay, days	
Mean	2.3±2.8
Median	1.0 (0-19)
Coils per procedure, number	
Mean	9.8±1.4
Median	10 (5-15)
Total coils implanted	1125
Upper, right Lobe	437
Upper, left Lobe	450
Lower, right Lobe	110
Lower, left Lobe	121
Middle, right Lobe	7
Coil implant Size	
70 mm	5
85 mm	20
100 mm	508
125 mm	462
150 mm	101
175 mm	28
200 mm	1

Data are shown as numbers, mean ± standard deviation, or median (minimum-maximum).

Safety

No periprocedural serious adverse events occurred in the 115 bronchoscopies performed under general anesthesia. No death or respiratory failure was reported. A summary of all serious and non-serious respiratory adverse events is listed in table 3. All events were treated and resolved with routine medical care and without sequelae.

Table 3. Adverse events.

	Treatment – 1 month		**> 1 month - 6 months**		**> 6 months - 12months**	
	events	patients	**events**	patients	**events**	patients
Serious respiratory adverse events						
COPD exacerbation	**7**	7	**12**	10	**4**	3
Pneumonia	**6**	5	**3**	3	**6**	6
Haemoptysis	**1**	1	**0**	0	**0**	0
Pneumothorax	**4**	4	**2**	2	**1**	1
Respiratory adverse events						
COPD exacerbation	**8**	7	**21**	15	**19**	15
Pneumonia	**5**	3	**4**	3	**3**	3
Mild haemoptysis (<5mL)	**61**	35	**3**	3	**2**	2
Cough	**2**	2	**3**	3	**0**	0
Transient chest pain	**28**	20	**7**	6	**3**	3

Adverse events presented per procedure for the first month after each procedure (115 procedures in total), for patients in the 1–6 month follow-up period (N=58) and for patients in the 6–12 month follow-up period (N=35). Events reported for both unilateral and bilateral treated patients.

Efficacy all patients
Of the 60 patients who were treated, 58 patients were evaluable at 6 months and 35 patients at 12 months (23 patients from Germany exited the study at 6 months). Because the German cohort exited the study at 6 months, we segregated the data to compare patients with 1-year follow-up data against their own 6 month results to analyze the sustainability of the clinical improvements within the same population (table 4). Across key clinical parameters, FEV_1 % predicted, residual volume % predicted and SGRQ results were sustained while mean distance on 6 minute walk test actually improved between 6 and 12 months. The minimal clinically important difference responder percentages for FEV_1, residual volume, distance on 6 minute walk test and SGRQ are shown in table 5.

Efficacy unilateral patients
Five patients were treated unilaterally. The reasons for treating only one lung were: lost to follow-up in two patients; second lung on second look not suitable for treatment (bullae) in one patient; and second lung declined by two patients (one improved satisfactory and one did not want to proceed with the trial). At 6 month follow-up in four evaluable patients, the median change in FEV_1 was +4.7% (range −17.8 to +17.0%), median change in distance on 6 minute walk test was +29 meter (range −46 to +92 meter) and residual volume and ratio of residual volume to total lung capacity remained stable.

Heterogeneous versus homogeneous disease
In the 33 bilaterally treated patients with 12 months follow-up, the post-hoc visual qualitative CT score of the degree of tissue destruction classified 20 patients as heterogeneous and 13 as homogeneous. When using the CT software analysis, 16 patients were classified as heterogeneous and 17 as homogeneous. Regardless of the classification method, both heterogeneous and homogeneous patients showed significant improvement at 1 year follow-up (table 6).

Upper versus lower lobe disease
In this trial lower lobe treatment was performed in 10 patients, of whom nine could be evaluated at the 6 month endpoint. Except for FEV_1 (+0.04±0.08 Liter for lower lobe versus +0.15±0.23 Liter for upper lobe; P=0.026), there were no statistically significant differences in the clinical responses between patients with upper versus lower lobe disease for residual volume, distance on 6 minute walk test and SGRQ.

Responder analysis
To identify lung volume reduction coil treatment responders we performed a multivariable analysis for the primary endpoint SGRQ and for the distance on 6 minute walk test. None of the input regressors (residual volume % of predicted value, ratio of residual volume to total lung capacity, FEV_1 % of predicted value, forced vital capacity, age, carbon monoxide lung transfer factor and emphysema type) were useful in associating patient outcomes at 6 months follow-up.

Table 4. Efficacy results at 6 months and 12 months of follow-up.

	Overall group (N=58) at 6 months of follow up	12 months FU group (N=34) at 6 months of follow up	12 months FU group (N=34) at 12 months of follow up
FEV_1, Liter	+0.11±0.20 (N=54, P<0.001)	+0.12±0.28 (N=33, P=0.021)	+0.11±0.30 (N=34, P=0.037)
FEV_1, %	+15±27 (N=54, P<0.001)	+18±32 (N=33, P=0.003)	+16±36 (N=34, P=0.017)
FVC, Liter	+0.20±0.53 (N=54, P=0.008)	+0.33±0.57 (N=33, P=0.0020	+0.28±0.45 (N=34, P=0.001)
RV, Liter	-0.65±0.90 (N=58, P<0.001)	-0.80±1.03 (N=34, p<0.001)	-0.71±0.81 (N=34, P<0.001)
RV, %	-11±15 (N=58, P<0.001)	-14±15 (N=34, P<0.001)	-14±13 (N=34, P<0.001)
Ratio of RV to TLC, %	-5±12 (N=58, P<0.007)	-6±9 (N=34, P<0.001)	-3±19 (N=34, P=0.245)
Distance on 6 minute walk test, meter	+30±74 (N=56, P=0.004)	+42±74 (N=34, P=0.002)	+51±76 (N=32, P=0.003)
SGRQ, points	-12±13 (N=56, P<0.001)	-10±16 (N=33, P<0.001)	-11±13 (N=32, P<0.001)
mMRC, points	-0.6±1.2 (N=58, P<0.001)	-0.8±0.9 (N=34, P<0.001)	-0.7±0.8 (N=34, P<0.001)

Efficacy at 6 months for all lung volume reduction coil treatments (N=58, overall group) and at 6 and 12 months (N=34, 12 month follow-up group columns). Results are given as change from baseline. Data are shown as mean ± standard deviation. Data in parentheses are the numbers of actual measurements available per variable tested followed by the actual P value. FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; mMRC, modified Medical Research Council dyspnea score; RV, residual volume; SGRQ, St George's Respiratory Questionnaire total score; TLC, total lung capacity.

Table 5. Responder rates at 6 months and 12 months.

	MCID	6 months	12 months
Forced expiratory volume in 1 second	**≥ 12%**[11]	48%	41%
Residual volume	**≥ 0.35**[12]	65%	58%
Distance on 6 minute walk test	**≥ 26 meter**[13]	53%	60%
St. George's respiratory questionnaire	**≥ 4 points**[14]	74%	66%
St. George's respiratory questionnaire	**≥ 8 points**	61%	53%

Responder rates at 6 and 12 months after bilateral lung volume reduction coil treatment using minimal clinically important differences (MCID). Results are given as percentage of responders to total patients.

Table 6. Results at 12 months after bilateral lung volume reduction coil treatment for patients classified as heterogeneous and homogeneous emphysema.

	Visual CT assessment at 12 months of follow up		
	Heterogeneous (N=20)	**Homogeneous (N=13)**	**P value**
FEV_1, Liter	+0.14±0.30	+0.08±0.28	ns
Residual volume, Liter	-0.69±0.87	-0.68±0.46	ns
Distance on 6 minute walk test, meter	+54±65	+46±68	ns
SGRQ, points	-13±15	-7±9	ns

	Digital CT assessment at 12 months of follow up		
	Heterogeneous (N=16)	**Homogeneous (N=17)**	**P value**
FEV_1, Liter	+0.18±0.32	+0.05±0.26	ns
Residual volume, Liter	-0.75±0.78	-0.66±0.72	ns
Distance on 6 minute walk test, meter	+75±67	+28±58	0.05
SGRQ, points	-12±14	-9±13	ns

Results are given as mean ± standard deviation in change from baseline. Heterogeneity and homogeneity were assessed by both a visual CT assessment (a 4-point qualitative score of the degree of tissue destruction where a difference of ≤1 point for both lungs was regarded as homogeneous) and a digital CT assessment (where the software calculated the percentage area of destruction at –950 Hounsfield units; a difference of ≤25% in destruction for both lungs was regarded as homogeneous). *P<0.05 for all end-points compared to baseline.

DISCUSSION

This prospective multicenter study assessed the long-term safety and improvements in patient-related outcome measures of lung volume reduction coil treatment in 60 patients with severe emphysema. The results show an acceptable safety profile associated with a significant and sustained improvement over 12 months in relevant clinical and functional parameters including FEV_1, residual volume, distance on 6 minute walk test and SGRQ.

This is the largest lung volume reduction coil study to date, and also evaluated longer-term results of lung volume reduction coil treatment. In our first pilot study (N=16) using the current treatment approach (median 10 coils per lung) and coil design, significant clinical and functional improvements were seen at 6 months including SGRQ (−14.9 points), FEV_1 (+14.9%), residual volume (−11.4%) and distance on 6 minute walk test (+84 meter) with an acceptable safety profile.[10] Recently, Shah et al[19] reported the results at 90 days after bilateral lung volume reduction coil treatment for 46 patients included in a randomized controlled study and demonstrated a significant improvement in SGRQ (−8.1 points), FEV_1 (+14%), residual volume (−0.51 Liter) and distance on 6 minute walk test (+51 meter), with no difference in serious adverse events between treatment and control groups.

In the present multicenter study involving 11 centers, no serious adverse events were reported during the lung volume reduction coil treatment procedures, demonstrating procedural safety. Serious adverse events (table 3) mainly occurred in the 30 days after the procedure, with all events resolving with regular medical care and without sequelae. Our results confirm the acceptable safety profile for lung volume reduction coil treatment with a rate of adverse events similar to previous reports on lung volume reduction coil treatment.[10,19] The rate of post-procedure exacerbations and pneumonia is comparable to reported events with endobronchial one-way valves.[6,8] Importantly, the total rate of these COPD-related events following endoscopic implants did not exceed the number of exacerbations and pneumonia that were reported in the EASE trial sham bronchoscopy control group.[20] Lung volume reduction coil specific procedure-induced events that occur are typically very mild hemoptysis or colored sputum requiring no intervention in about 50% of subjects and temporary chest discomfort for a few days requiring either a standard painkiller regimen for a few days or no intervention at all in about one-third of subjects treated.

Regarding efficacy, our results show significant improvements in clinical and functional parameters at 6 months with a magnitude of response in line with the two recent reports on lung volume reduction coil treatment,[10,19] reporting on 6 month and 3 month follow-up, respectively. Our study provides the first longer-term analysis of data over 12 months after bilateral lung volume reduction coil treatment and demonstrates a sustained response at 12 months. To better analyze the relevance of the efficacy results, we analyzed the minimal clinically important difference in FEV_1,[11] residual volume,[12] distance on 6 minute walk test,[13] and SGRQ[14] and found a significant responder rate at 6 and 12 months for these clinical endpoints (table 5).

The cohort trial design can, of course, induce bias. However, the results reported are higher than reported minimal clinically important difference for our endpoints and show similar efficacy across multiple centers. Furthermore, we have previously shown that, even in a sham controlled bronchoscopic interventional trial design, no real placebo effect could be observed in patients with severe COPD.[20]

To better understand the predictors of response to lung volume reduction coil treatment, we conducted a multivariate analysis to assess the relationship between the response to treatment and baseline variables typically identified as predictors of outcome, such as hyperinflation and emphysema heterogeneity. Using the 6 month endpoints, none of the evaluated baseline variables provided a meaningful predictor of response to lung volume reduction coil treatment. Other potential variables could include nuanced emphysema phenotypes beyond heterogeneous or homogeneous classification, such as more or less small airways disease, centrilobular versus panlobular emphysema and variability in placement strategies including proximal versus distal placement within the sub-segmental airways and/or the number and size of coils deployed. The current active clinical trials (NCT01822795[21] and NCT01608490) and future meta-analysis data of patients treated in the four European clinical studies thus far may increase the statistical power sufficiently to perform this analysis better. In our study, where broad selection criteria were purposely used in order to evaluate the effectiveness in a population of patients representative of the patients we see in daily practice, we found a large variability of response between patients. However, responder rates overall for several endpoints were already high (table 5). The difficulty of identifying strong predictors of success has been previously demonstrated by a predictive multivariate effort completed in a much larger patient cohort (N=608) for outcome after lung volume reduction surgery. In this large group, only a very weak signal for the ratio of residual volume to total lung capacity and emphysema distribution could be demonstrated.[22]

Lung hyperinflation is a major feature of emphysema and is associated with dyspnea, exercise intolerance and compromised daily physical activity.[23,24] In this study, neither baseline residual volume nor the ratio of residual volume to total lung capacity as % of predicted value the response to lung volume reduction coil treatment. This is possibly due to the fact that residual volume greater than 175% of predicted value was an inclusion criterion, resulting in treatment of severe static hyperinflated patients (mean baseline residual volume 249±53% of predicted value). On the other hand, the magnitude of change in residual volume after lung volume reduction coil treatment was associated with more favorable mean clinical and functional outcomes in this study, suggesting that residual volume changes may be viewed as a marker of response to treatment and that, by selecting patients with more potential for significant residual volume decrease, the likelihood of significant clinical benefit may be increased. The finding that residual volume is reduced by lung volume reduction coil treatment might be related to mechanical volume compression of lung tissue exerted by the coils, as well as improvement in elastic recoil achieved by decreasing airway resistance.[25]

When comparing the results for patients with upper lobe versus lower lobe treatment, no outcome differences were observed for residual volume, distance on 6 minute walk test

and SGRQ. The lower FEV_1 results seen with lower lobe coil treatments is comparable to the experience with lung volume reduction surgery in the lower lobes where the effect on improving FEV_1 is also limited compared with other outcome variables.[26] However, because FEV_1 in general shows poor correlation with performance in patients with severe emphysema,[27] and that patient-relevant outcomes such as distance on 6 minute walk test and SGRQ show strong improvement even in lower lobe subjects, lower lobe treatment with coils appears to be a clinically valid treatment option with clear patient benefit. Future work will evaluate whether, as currently hypothesized, the much bigger lower lobes require a greater number of coils to optimize results.

Our post-hoc CT analysis showed that a large number of patients were classified as homogeneous when using both a visual and a digital assessment, even though the inclusion criteria called for heterogeneous patients per clinicians' visual assessment. This finding should be cautiously considered, since this trial was not designed to prospectively identify homogeneous emphysema patients and the two methods of creating a heterogeneous versus a homogeneous group are arbitrary. Our results show that lung volume reduction coil treatment also benefits patients with less pronounced heterogeneous to homogeneous disease. Our data showed a statistically and clinically significant benefit for both groups compared with baseline, with overall a potentially increased mean efficacy for the heterogeneous patient group. The fact that lung volume reduction coil treatment also shows efficacy in patients with homogeneous emphysema is a very important finding, challenging the assumption that only patients with heterogeneous emphysema will respond to lung volume reduction coil treatment, as has been shown for surgical lung volume reduction[28] and endobronchial valve treatment.[6,7] Of note, other bronchoscopic techniques such as thermal vapor ablation[29] and sealant therapy[30] are also restricted to upper lobe predominant heterogeneous emphysema, leaving a broad group of patients with non-upper lobe predominant and homogeneous disease without a treatment option. It can be hypothesized that lung volume reduction coil treatment is similarly efficient in both heterogeneous and homogeneous emphysema because of a different mechanism of action from true 'lung volume reducing' therapies, as the primary mechanism of action of coils appears to be mechanical re-tensioning of the airway network rather than just reducing absolute lung volume alone. However, additional studies are necessary to better characterize the mechanisms of action of coils and also to confirm the efficacy of lung volume reduction coil treatment in homogeneous emphysema, which represents a large number of patients usually excluded from other surgical and bronchoscopic lung volume reduction treatment options.

CONCLUSION

This study provides multicenter evidence for the feasibility, procedural safety and efficacy of lung volume reduction coil treatment in patients with both heterogeneous and homogeneous emphysema. Further studies are underway to confirm efficacy in long-term randomized trials. Additional studies are needed to improve the understanding of the predictive factors of response in order to better select the responders to lung volume reduction coil treatment.

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