Preliminary Communication

Lung Volume Reduction Coil Treatment vs Usual Care in Patients With Severe Emphysema
The REVOLENS Randomized Clinical Trial

Gaëtan Deslée, MD, PhD; Hervé Mal, MD, PhD; Hervé Dutau, MD, PhD; Arnaud Bourdin, MD, PhD; Jean Michel Vergnon, MD, PhD; Christophe Pison, MD, PhD; Romain Kessler, MD, PhD; Vincent Jounieaux, MD, PhD; Luc Thiberville, MD, PhD; Sylvie Leroy, MD; Armelle Marceau, MD; Sophie Laroumagne, MD; Jean Pierre Mallet, MD; Sylvain Dukic, PhD; Coralie Barbe, MD; Julie Bulsei, PharmD; Damien Jolly, MD, PhD; Isabelle Durand-Zaleski, MD, PhD; Charles Hugo Marquette, MD, PhD; for the REVOLENS Study Group

IMPORTANCE Therapeutic options for severe emphysema are limited. Lung volume reduction using nitinol coils is a bronchoscopic intervention inducing regional parenchymal volume reduction and restoring lung recoil.

OBJECTIVE To evaluate the efficacy, safety, cost, and cost-effectiveness of nitinol coils in treatment of severe emphysema.

DESIGN, SETTING, AND PARTICIPANTS Multicenter 1:1 randomized superiority trial comparing coils with usual care at 10 university hospitals in France. Enrollment of patients with emphysema occurred from March to October 2013, with 12-month follow-up (last follow-up, December 2014).

INTERVENTIONS Patients randomized to usual care (n = 50) received rehabilitation and bronchodilators with or without inhaled corticosteroids and oxygen; those randomized to bilateral coil treatment (n = 50) received usual care plus additional therapy in which approximately 10 coils per lobe were placed in 2 bilateral lobes in 2 procedures.

MAIN OUTCOMES AND MEASURES The primary outcome was improvement of at least 54 m in the 6-minute walk test at 6 months (1-sided hypothesis test). Secondary outcomes included changes at 6 and 12 months in the 6-minute walk test, lung function, quality of life as assessed by St George's Respiratory Questionnaire (range, 0-100; 0 being the best and 100 being the worst quality of life; minimal clinically important difference, ≥4), morbidity, mortality, total cost, and cost-effectiveness.

RESULTS Among 100 patients, 71 men and 29 women (mean age, 62 years) were included. At 6 months, improvement of at least 54 m was observed in 18 patients (36%) in the coil group and 9 patients (18%) in the usual care group, for a between-group difference of 18% (1-sided 95% CI, 4% to ∞; $P = .03$). Mean between-group differences at 6 and 12 months in the coil and usual care groups were +0.09 L (95% CI, 0.05 L to ∞) ($P = .001$) and +0.08 L (95% CI, 0.03 L to ∞) ($P = .002$) for forced expiratory volume in the first second, +21 m (95% CI, −4 m to ∞) ($P = .06$) and +21 m (95% CI, −5 m to ∞) ($P = .12$) for 6-minute walk distance, and −13.4 points (95% CI, −8 points to ∞) and −10.6 points (95% CI, −5.8 points to ∞) for St George's Respiratory Questionnaire (1-sided $P < .001$ for both). Within 12 months, 4 deaths occurred in the coil group and 3 in the usual care group. The mean total 1-year per-patient cost difference between groups was $47 908 (95% CI, $47 879-$48 073) ($P < .001$); the incremental cost-effectiveness ratio was $782 598 per additional quality-adjusted life-year.

CONCLUSIONS AND RELEVANCE In this preliminary study of patients with severe emphysema followed up for 6 months, bronchoscopic treatment with nitinol coils compared with usual care resulted in improved exercise capacity with high short-term costs. Further investigation is needed to assess durability of benefit and long-term cost implications.

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: Members of the REVOLENS Study Group are listed at the end of this article.

Corresponding Author: Gaëtan Deslée, MD, PhD, Service de Pneumologie, INSERM U903, Hôpital Universitaire de Reims, 45 Rue Cognacq-Jay, 51092 Reims, France (gdeslee@chu-reims.fr).

Emphysema, a key component of chronic obstructive pulmonary disease, is characterized by lung tissue inelasticity, air trapping, and hyperinflation, causing dyspnea, exercise limitation, and impaired quality of life. Management of severe emphysema represents a challenge because of limited efficacy of currently available treatments. Lung volume reduction surgery demonstrated improved overall survival and better clinical and functional outcomes, particularly in patients with upper lobe–predominant emphysema and low exercise capacity.[1,2] However, lung volume reduction surgery is associated with significant morbidity and mortality. A number of minimally invasive interventional strategies, including endobronchial valves,[3,4] airway bypass,[5] biological sealants,[6] thermal vapor ablation,[7] and endobronchial coils,[8-14] have been evaluated. Endobronchial valves showed clinically significant improvements in selected patients with upper lobe–predominant emphysema[4] and with intact fissures.[3,4]

FEV_1 *forced expiratory volume in the first second*

FVC *forced vital capacity*

QALY *quality-adjusted life-year*

RV *residual volume*

TLC *total lung capacity*

Shape-memory nitinol coils are nonblocking devices bronchoscopically delivered into subsegmental airways to induce regional parenchymal volume reduction, enhance lung recoil, and reestablish small airway tethering. To date, coils have been investigated in 5 nonrandomized studies[8-11,13] and 1 randomized, controlled 90-day crossover study.[12,14] These studies reported that coil treatment provided improvement in quality of life, exercise capacity, and lung function.

High costs are associated with lung volume reduction strategies for severe emphysema.[2,15] Acceptance of new therapies should consider evidence of cost-effectiveness. Because the health economic evidence base for bronchoscopic interventional strategies is minimal,[15] the current study design included a cost-effectiveness analysis.

The REVOLENS trial (Réduction Volumique Endobronchique par Spirales) was designed to evaluate the efficacy, safety, cost, and cost-effectiveness of coil treatment in severe emphysema.

Methods

Study Oversight

Ten sites throughout France participated in the study. This study was approved by the Ethics Committee of Dijon Est I and by the French Agency for Medicines and Health Products. A website was accessible to participants and referring physicians (http://www.euroemphysema.com). Enrollment of participants started in March 2013 and was completed in October 2013. The last follow-up visit was in December 2014. An independent data and safety monitoring board monitored events and reviewed efficacy results. The trial protocol has been previously published[16] and is available in Supplement 1. All participants provided written informed consent.

Patient Population and Randomization

Eligible patients were randomized in a 1:1 fashion to receive usual care or coils using a centralized computer-generated randomization system with fixed blocks of 4. The main inclusion criteria were bilateral emphysema, postbronchodilator forced expiratory volume in the first second (FEV_1) of less than 50% predicted, residual volume (RV) of greater than 220% predicted, and formal pulmonary rehabilitation within the previous 12 months (eBox in Supplement 2).

Emphysema was quantified in each lobe using the National Emphysema Treatment Trial visual assessment score.[17] The most severely affected lobe of each lung was targeted for coil treatment and the upper lobe was chosen when ipsilateral scores were the same. Scoring and targeting were determined by each site. No computed tomography densitometry analysis was used in this study.

Usual Care Group

Patients were treated at the discretion of the patient's physician in compliance with international guidelines; ie, they received prerandomization rehabilitation, inhaled bronchodilators, and influenza and pneumococcal vaccination, with or without inhaled corticosteroids and with or without oxygen, according to the degree of severity and exacerbation rate.

Intervention Coil Group

Patients in the coil group received the same treatment as the usual care group and also received coil treatment within 15 days after randomization. The contralateral treatment was completed 1 to 3 months after the first. All coil insertion procedures were conducted under general anesthesia using fluoroscopy to guide placement (eFigures 1 and 2 in Supplement 2). Two sizes of coil (100 mm and 125 mm; PneumRx/BTG) were available. Approximately 10 coils per targeted lobe were delivered. The coil group received amoxicillin/clavulanic acid, 2 g (or clindamycin, 600 mg, and gentamycin, 5 mg/kg, if allergic to amoxicillin), immediately before the procedure. Chest radiography was performed within 2 hours of and at 24 hours after the procedure (eFigure 3 in Supplement 2). In the absence of significant complications, patients were discharged at the discretion of the attending physician.

Follow-up

All patients were assessed at baseline and at 1, 3, 6, and 12 months after baseline. All patients underwent medical examination, 6-minute walk test on room air, chest x-ray, and pulmonary function tests according to international guidelines.[18] Patients completed dyspnea questionnaires using the modified Medical Research Council dyspnea scale and the Baseline Dyspnea Index/Transition Dyspnea Index. The modified Medical Research Council dyspnea scale grades 5 different levels of dyspnea based on the circumstances in which it arises: grade 0, "I only get breathless with strenuous exercise"; grade 1, "I get short of breath when hurrying on level ground or walking up a slight hill"; grade 2, "On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on the level"; grade 3, "I stop for breath after walking about 100 yards or after a few minutes on level ground"; grade 4, "I am too breathless to leave the house or I am breathless when dressing." Quality of life was assessed using the St George's Respiratory Questionnaire, ranging from 0 to 100 with higher scores

indicating worse quality of life (0 being the best and 100 being the worst quality of life, and −4 points considered a minimal clinically important difference), and the EuroQol 5 Dimensions Questionnaire provided a utility value on a scale ranging from 0 (death) to 1 (full health). All patients had a thoracic computed tomography scan at baseline and the coil group also had one at 6 months. Medications and oxygen use were recorded at each visit. Patients in both groups continued their regular treatment.

Study End Points

The primary outcome was improvement of at least 54 m in the 6-minute walk test at 6 months. The cutoff to define a responder was based on data from Redelmeier et al[19] showing that the distances needed to differ by 54 m for the average patient to stop rating themselves as "about the same" and start rating themselves as either "a little bit better" or "a little bit worse." Secondary end points were changes at 6 and 12 months from baseline in the 6-minute walk distance, pulmonary function tests (FEV_1, forced vital capacity [FVC], RV, total lung capacity [TLC], and RV/TLC), dyspnea (modified Medical Research Council dyspnea scale and Baseline Dyspnea Index/Transition Dyspnea Index), and quality of life (St George's Respiratory Questionnaire and EuroQol 5 Dimensions Questionnaire) in each group.

The safety outcomes included all nonserious and serious adverse events. In the coil group, serious adverse events were stratified by occurrence within 30 days vs after 30 days to 12 months. A composite score included any of the following serious adverse events occurring within 24 hours after treatment: death, pneumothorax requiring chest tube placement for more than 7 days or surgical treatment, hemoptysis greater than 150 mL, and invasive ventilation for more than 24 hours. A second composite score also included the following serious adverse events occurring within 12 months in both groups: death, hemoptysis greater than 150 mL, pneumonia requiring hospitalization, pneumothorax requiring chest tube placement for more than 7 days or surgical treatment, invasive ventilation for more than 24 hours, and lung transplantation.

Economic Evaluation

The prospective economic evaluation was concurrent with the randomized trial, in accordance with the CHEERS statement.[20] The prospective analysis was conducted from the health care perspective to determine the cost per quality-adjusted life-year (QALY) gained with coils compared with usual care over a 1-year period. Both hospital and nonhospital resources were considered. Procedure costs for coil treatment were obtained with a bottom-up microcosting approach that identified all relevant cost components of the procedure and valued each component for all individual patients using duration of the procedure, staff, medical devices, and type of operating room as variables. Unit costs are presented in eTable 1 in Supplement 2. All costs are in 2014 US dollars (US $1 = €0.754 in 2014) and are not discounted because of the short time horizon.

Health outcomes are valued in QALYs. Health-related quality of life was assessed using the EuroQol 5 Dimensions self-administered questionnaires at baseline, 6 months, and 1 year. The utility values are based on French tariffs for the corresponding EuroQol 5 Dimensions scores. Utility curves were obtained for each group by plotting average utility values at baseline, 6 months, and 1 year. The difference in QALYs was estimated as the difference in the area between the utility curves for the 2 groups.

A cost-effectiveness analysis was conducted to estimate incremental costs per incremental QALY. Incremental costs were taken as the difference in per-patient costs between groups.

Baseline characteristics, QALYs, and costs are described using counts (and proportions), means (with standard deviations or 95% confidence intervals), or medians (with interquartile ranges). Differences in costs and QALYs were tested using standard parametric or nonparametric tests (*t* test or Mann-Whitney test) as appropriate and are described as means (with 95% confidence intervals). The incremental cost difference and generated 95% confidence intervals were calculated using nonparametric bootstrapping with 1000 replications. An acceptability curve was generated based on the bootstrap results. Statistical significance for differences among a priori comparisons was set at $P = .05$ (2-sided).

Statistical Analyses

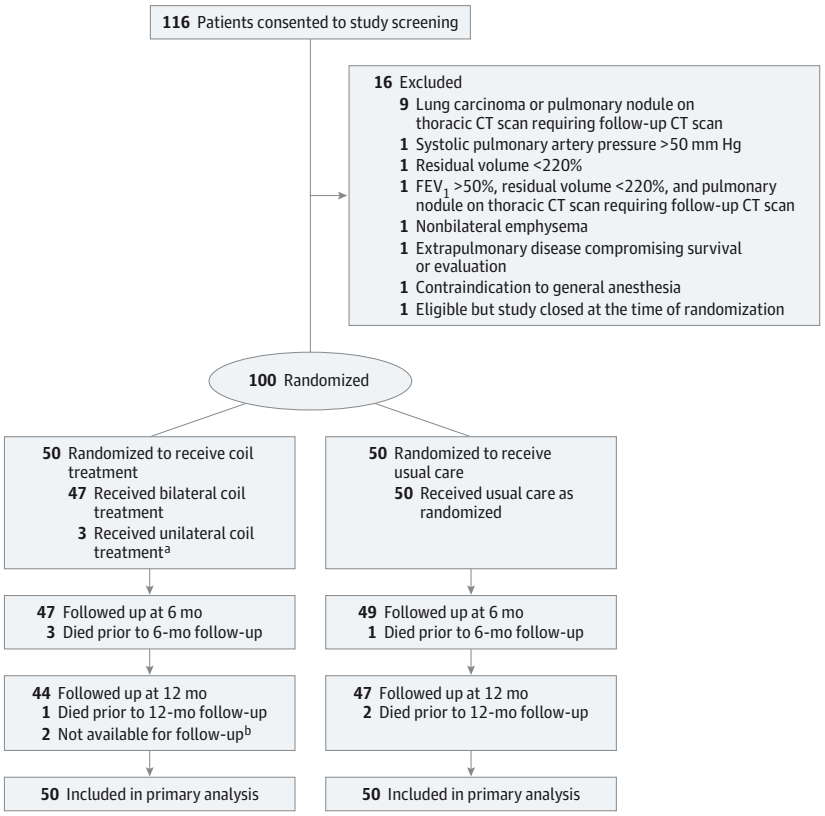
The statistical power to demonstrate a superior success rate (1-sided hypothesis test) in the primary end point for the coil group vs the usual care group was anticipated to be 90% with a significance of $\alpha = .05$ at a total sample size of 100 patients, based on the hypothesis of a 37% end-point achievement in the coil group and 5% in the usual care group and with 30% of patients unable to perform the 6-minute walk test or lost to follow-up at 6 months. The hypothesis of a 37% primary end-point achievement in the coil group was based on data provided by PneumRx in 2012. One-sided statistical tests were considered appropriate in view of the favorable results of previous smaller studies[9-14,21] and confirmed by a recent meta-analysis.[22] The sample size was calculated using Nquery software, version 7.0 (Statistical Solutions Ltd).

Variables are presented using means with standard deviations or raw numbers and percentages. Differences at baseline between groups were analyzed using the χ^2 test, *t* test, or Fisher exact test.

For the primary end point, intention-to-treat analyses were conducted using a multiple imputation method for missing data using SAS procedures PROC MI and PROC MIANALYSE (SAS version 9.3, SAS Institute Inc). A logit model was used to impute the outcome for participants who did not perform the 6-minute walk test at 6 months, based on the parameters of FEV_1, FVC, RV, St George's Respiratory Questionnaire total score, modified Medical Research Council dyspnea scale, and Baseline Dyspnea Index/Transition Dyspnea Index. Ten imputations were performed. Bivariable logistic models were then fitted with the imputed values using treatment group as the predictor variable. An additional maximum bias analysis considering patients who did not perform the 6-minute walk test to be nonresponders for the primary end point was also conducted.

The secondary end points for efficacy (1-sided test) and safety (2-sided test) outcomes were analyzed using the χ^2 test, *t* test, or Fisher exact test, or Wilcoxon test when applicable, with no data imputation. For quantitative end points, mean differences and 1-sided 95% confidence intervals were reported. All end points were assessed by intention-to-treat analysis.

Figure. Flow of Participants in the REVOLENS Study



CT indicates computed tomography; FEV_1, forced expiratory volume in the first second.

[a] The reasons for not performing bilateral treatment were death before second treatment (n = 1), anaphylactic shock at induction of anesthesia for the second coil treatment (n = 1) (further analyses demonstrated allergy to penicillin), and pneumonia after the first coil treatment leading to unwillingness of the patient to undergo a second coil treatment (n = 1).

[b] These 2 patients were alive at 12 months but did not attend the planned visit at 12 months.

An independent data monitoring team ensured 100% source verification of the data. Statistical analyses were performed according to a prespecified statistical analysis plan (available in Supplement 3). No intermediary statistical analyses were conducted. A 1-sided $P < .05$ was considered statistically significant for the efficacy analysis. No adjustment of significance level was used for the secondary end points, which were then exploratory. A 2-sided $P < .05$ was considered statistically significant for baseline between-group comparisons and for safety analyses. SAS software, version 9.3 (SAS Institute Inc) was used for statistical analysis.

Results

Patients and Procedures

Of 116 patients who consented, 100 patients were randomized to the coil (n = 50) or usual care (n = 50) groups (**Figure**). Baseline characteristics are shown in **Table 1**. Among the 50 patients randomized to the coil group, 47 patients received bilateral and 3 received unilateral coil treatment (Figure), for a total of 97 procedures (eTable 3 in Supplement 2). A mean of 9.8 (SD, 1.3) coils per procedure were placed. The mean procedure time was 54 (SD, 17) minutes.

Primary End Point

Six-minute walk test results were available for 44 patients in each group at 6 months. Sixteen patients in the coil group and 8 patients in the usual care group achieved a 6-minute walk test improvement of at least 54 m at 6 months. Using multiple imputation for missing data, 18 patients (36%) in the coil group and 9 patients (18%) in the usual care group achieved a 6-minute walk test improvement of at least 54 m at 6 months ($P = .03$), with a mean between-group difference of 18% (95% CI, 4% to ∞) (**Table 2** and eFigure 4 in Supplement 2). In a maximum bias analysis considering patients who did not perform the 6-minute walk test to be nonresponders for the primary end point, the P value was .03. The primary end point was therefore achieved.

Secondary Efficacy End Points

The secondary efficacy end points at 6 and 12 months are shown in Table 2. At 6 months, improvements from baseline were significant in the coil group compared with the usual care group in the 6-minute walk test (when analyzed as percent change but not when analyzed by distance walked), FEV_1, FVC, RV, RV/TLC, modified Medical Research Council dyspnea scale, Transition Dyspnea Index, and St George's Respiratory Questionnaire (all $P < .05$). At 12 months, improvements from baseline were significant in the coil group compared with the usual care group for FEV_1, FVC, RV, RV/TLC, modified Medical Research Council dyspnea scale, and St George's Respiratory Questionnaire (all $P < .05$) but not for the 6-minute walk test.

Quantitatively, the mean between-group differences for the secondary end points in the coil and usual care groups were at 6 and 12 months, respectively, 11% (95% CI, 6% to ∞; $P = .001$) and 11% (95% CI, 5.2% to ∞; $P = .002$) for FEV_1, −7% (95% CI,

Table 1. Baseline Participant Characteristics[a]

Characteristics	Coil Treatment (n = 50)	Usual Care (n = 50)
Age, y	62.1 (8.3)	61.9 (7.3)
Men, No. (%)	39 (78)	32 (64)
Pack-years smoked	44 (19)	46 (21)
Body mass index[b]	22.5 (4.1)	23 (4.3)
6-Minute walk test distance, m	300 (112)[c]	326 (121)
Modified Medical Research Council dyspnea scale score, No. (%)[d]		
1	0	1 (2)[e]
2	11 (22)	13 (26)
3	28 (56)	25 (50)
4	11 (22)	11 (22)
Baseline Dyspnea Index score[f]	4.4 (2.1)	4.1 (1.9)
FEV_1, % predicted	25.7 (7.5)	27.4 (6.2)
FEV_1, L	0.75 (0.25)	0.77 (0.22)
FVC, % predicted	67.4 (16.5)	72 (20.1)
FVC, L	2.45 (0.61)	2.53 (0.82)
FEV_1/FVC ratio	0.31 (0.09)	0.32 (0.08)
RV, % predicted	271.2 (38.1)	269.3 (44.3)
RV, L	6.2 (0.86)	6 (1.18)
TLC, % predicted	141.7 (16.6)	143.6 (18)
TLC, L	8.85 (1.03)	8.66 (1.35)
RV/TLC ratio	0.70 (0.06)	0.69 (0.07)
St George's Respiratory Questionnaire score[g]		
Impact	49.4 (17.2)	44.9 (16.7)
Activity	81.8 (11.5)	78.5 (13.7)
Symptoms	58.2 (17.1)	56.2 (19.8)
Total	60.8 (12.8)	57.1 (14.1)
Emphysema score[h]		
Right upper lobe	2.9 (0.7)	3.2 (0.8)
Middle lobe	2.1 (1)	2.3 (0.8)
Right lower lobe	2.2 (0.9)	2.2 (0.8)
Left upper lobe	2.9 (0.8)	3 (0.7)
Left lower lobe	2.3 (0.9)	2.2 (1)
Heterogeneous, No. (%)[i]	17 (34)	16 (32)
Treatments, No. (%)		
Oxygen therapy	32 (64)	29 (58)
Long-action β-agonists	49 (98)	48 (96)
Long-acting muscarinic antagonists	45 (90)	42 (84)
Inhaled corticosteroids	46 (92)	43 (86)

Abbreviations: FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity.

[a] Values are shown as mean (SD) unless otherwise indicated. There were no between-group differences in baseline characteristics (2-sided test).

[b] Body mass index was calculated as weight in kilograms divided by height in meters squared.

[c] The 6-minute walk test was conducted with 1 patient receiving oxygen in error, and the patient was retained for further follow-up and included in analyses.

[d] The modified Medical Research Council dyspnea scale grades 5 different levels of dyspnea based on the circumstances in which it arises. See Methods section of text for description.

[e] One patient with a modified Medical Research Council dyspnea scale score of 1 was included in error but was included in the follow-up and analyses.

[f] The Baseline Dyspnea Index uses 5 grades (0-4) for 3 categories, functional impairment, magnitude of task, and magnitude of effort, with a total score of 0 to 12. Higher scores indicate less dyspnea.

[g] The St George's Respiratory Questionnaire (range, 0-100) has 3 component domains (impact, activity, and symptoms) measuring quality of life. Higher scores indicate worse quality of life.

[h] A visual score from 0 to 4 was assigned to each lobe, based on the extent of tissue destruction, where 0 = no emphysema, 1 = 1% to 25% emphysematous, 2 = 26% to 50%, 3 = 51% to 75%, and 4 = >75%.

[i] Emphysema was classified as heterogeneous if there was a difference of greater than 1 point between ipsilateral lobes.

−2% to −∞; P = .009) and −7% (95% CI, −2.6% to −∞; P = .003) for RV, 8% (95% CI, −2.7% to ∞; P = .048) and 7.1% (95% CI, −2.2% to ∞; P = .09) for the 6-minute walk test, −13.4 points (95% CI, −8 points to −∞; P < .001) and −10.6 points (95% CI, −5.8 points to −∞; P < .001) for quality of life assessed by the St George's Respiratory Questionnaire, −0.45 units (95% CI, −0.17 units to −∞; P = .01) and −0.4 units (95% CI, −0.05 units to −∞; P = .02) for dyspnea assessed by the modified Medical Research Council scale, and 1.6 points (95% CI, 0.54 points to ∞; P = .04) and 1.1 points (95% CI, −0.5 points to ∞; P = .08) for the Transition Dyspnea Index.

A post hoc analysis did not find any difference regarding efficacy between homogeneous and heterogeneous emphysema (eTable 2 in Supplement 2).

Safety Outcomes

Serious adverse events are presented in **Table 3** and nonserious adverse events are presented in eTable 4 in Supplement 2. Pneumonia was the most frequent serious adverse events, including 11 events in 9 patients (18%) in the coil group and 2 events in 2 patients (4%) in the usual care group within 1 year, with a difference between groups of 14% (95% CI, 2%-26%; P = .03). Overall, at least 1 serious adverse event occurred within 1 year in 26 patients (52%) in the coil group and in 19 patients (38%) in the usual care group, with a between-group difference of 14% (95% CI, −5% to 33%; P = .16). The serious adverse event composite score within 12 months included 17 events in 14 patients (28%) in the coil group and 8 events in 6 patients (12%) in the usual care group, with a difference between groups of 16%

Table 2. Primary and Secondary Intention-to-Treat Efficacy End Points

Outcomes	Coil Treatment (n = 50)	Usual Care (n = 50)	Difference (1-Sided 95% CI)	*P* Value[a]
Primary End Point				
6-Minute walk test, ≥54 m improvement, No. (%)[b]	18 (36)	9 (18)	0.18 (0.04 to ∞)	.03
Secondary End Points at 6 mo, Mean (95% CI)				
6-Minute walk test improvement, m	18 (−6 to 43)	−3 (−22 to 16)	21 (−4 to ∞)	.06
% Change	9 (−1 to 20)	1 (−6 to 9)	8 (−2.7 to ∞)	.048
Dyspnea				
Modified Medical Research Council dyspnea scale score	−0.5 (−0.8 to −0.2)	−0.1 (−0.3 to 0.1)	−0.45 (−0.17 to −∞)	.01
Transition Dyspnea Index total score[c]	0.8 (−0.3 to 2.0)	−0.8 (−1.6 to 0)	1.6 (0.54 to ∞)	.04
Pulmonary function				
FEV_1, L	0.06 (0.02 to 0.11)	−0.03 (−0.05 to 0)	0.09 (0.05 to ∞)	.001
% Change	9 (4 to 14)	−3 (−6 to 1)	11 (6 to ∞)	.001
FVC, L	0.26 (0.11 to 0.40)	0.05 (−0.12 to 0.22)	0.21 (0.03 to ∞)	.03
% Change	15 (7 to 21)	5 (−2 to 12)	10 (1.5 to ∞)	.01
RV, L	−0.52 (−0.74 to −0.31)	−0.15 (−0.41 to 0.11)	−0.37 (−0.09 to −∞)	.01
% Change	−9 (−12 to −5)	−2 (−6 to 2)	−7 (−2 to −∞)	.009
TLC, L	−0.34 (−0.50 to −0.18)	−0.14 (−0.35 to 0.06)	−0.20 (0.03 to −∞)	.09
% Change	−4 (−6 to −2)	−2 (−4 to 1)	−2.0 (0.3 to −∞)	.10
RV/TLC ratio	−0.04 (−0.05 to −0.02)	−0.01 (−0.03 to 0.01)	−0.03 (−0.01 to −∞)	.01
% Change	−5 (−8 to −3)	−1 (−4 to 2)	−5.2 (−1.5 to −∞)	.01
Quality of life				
St George's Respiratory Questionnaire score				
Total	−11.1 (−15.9 to −6.2)	2.3 (−1.3 to 5.9)	−13.4 (−8 to −∞)	<.001
Impact	−12.5 (−18.1 to −6.8)	1.7 (−2.2 to 5.6)	−14.0 (−9 to −∞)	<.001
Activity	−11.3 (−16.3 to −6.2)	0.7 (−2.7 to 4.1)	−12.0 (−7 to −∞)	<.001
Symptoms	−4.7 (−11.5 to 2.1)	4.3 (−2.5 to 11.0)	−9.0 (−1.1 to −∞)	.04
Secondary End Points at 12 mo, Mean (95% CI)				
6-Minute walk test improvement, m	−2 (−29 to 25)	−23 (−42 to −4)	21 (−5 to ∞)	.12
% Change	−0.05 (−10 to 10)	−7.2 (−13 to −1)	7.1 (−2.2 to ∞)	.09
Dyspnea				
Modified Medical Research Council dyspnea scale score	−0.5 (−0.8 to −0.1)	−0.1 (−0.3 to −0.1)	−0.4 (−0.05 to −∞)	.02
Transition Dyspnea Index total score[c]	−0.2 (−1.9 to 1.4)	−1.3 (−2.2 to −0.3)	1.1 (−0.5 to ∞)	.08
Pulmonary function				
FEV_1, L	0.05 (0.01 to −0.10)	−0.03 (−0.06 to 0.01)	0.08 (0.03 to ∞)	.002
% Change	8 (3 to 13)	−3 (−8 to 2)	11 (5.2 to ∞)	.002
FVC, L	0.27 (0.12 to 0.43)	0 (−0.17 to 0.17)	0.27 (0.07 to ∞)	.008
% Change	14 (7 to 21)	4 (−3 to 9)	10 (2.4 to ∞)	.02
RV, L	−0.47 (−0.67 to −0.26)	−0.11 (−0.35 to 0.12)	−0.36 (−0.10 to −∞)	.004
% Change	−9 (−12 to −5)	−2 (−5 to 1)	−7 (−2.6 to −∞)	.003
TLC, L	−0.29 (−0.49 to −0.09)	−0.09 (−0.31 to 0.13)	−0.20 (0.04 to −∞)	.06
% Change	−3 (−5 to −1)	−1 (−3 to 1)	−2 (0.3 to −∞)	.06
RV/TLC ratio	−0.03 (−0.05 to −0.02)	0 (−0.02 to 0.01)	−0.03 (−0.01 to −∞)	.007
% Change	−5 (−7 to −2)	0 (−3 to 2)	−5 (−1.6 to −∞)	.008
Quality of life				
St George's Respiratory Questionnaire score				
Total	−9.1 (−14.1 to −4.2)	1.5 (−1.8 to 4.7)	−10.6 (−5.8 to −∞)	<.001
Impact	−10.8 (−16.4 to −5.1)	1.8 (−2.5 to 6.0))	−12.6 (−6.8 to −∞)	<.001
Activity	−9.4 (−11.3 to −4.4)	2.8 (0.0 to 5.6)	−12.2 (−7.5 to −∞)	<.001
Symptoms	−4.2 (−11.5 to 3.0)	−3.9 (−8.7 to 0.9)	−0.3 (6.7 to −∞)	.45

Abbreviations: FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity.

[a] One-sided testing (χ^2 or Wilcoxon W tests).

[b] Multiple imputation for missing data.

[c] The Transition Dyspnea Index evaluates changes from the Baseline Dyspnea Index. Higher scores indicate less dyspnea.

Table 3. Serious Adverse Events[a]

Events	Coil Treatment (n = 50)			Usual Care (n = 50)			
	Patients, No. (%)	No. of Events ≤30 d	No. of Events >30 d to 12 mo	Patients, No. (%)	No. of Events at 12 mo	Difference, % (95% CI)[b]	*P* Value
Chronic obstructive pulmonary disease exacerbation	13 (26)	4	12	11 (22)	13	4 (−13 to 21)	.64
Pneumothorax	3 (6)	3	1[c]	1 (2)	1	4 (−4 to 12)	.62
Hemoptysis	1 (2)	1	0	0	0	2 (−2 to 6)	.99
Thoracic pain	2 (4)	1	1	2 (4)	2	−2 (−9 to 5)	.99
Pneumonia	9 (18)	5	6	2 (4)	2	14 (2 to 26)	.03
Cardiovascular	1 (2)	1	0	3 (6)	3	−4 (−12 to 4)	.62
Other	8 (16)	2	7	6 (12)	7	4 (−10 to 18)	.56
Unknown	1 (2)	0	1	0	0	2 (−2 to 6)	.99
Total	26 (52)	17	28	19 (38)	28	14 (−5 to 33)	.16
Deaths	4 (8)	1[d]	3[e]	3 (6)[f]	3	2 (−8 to 12)	.99
Composite score within 24 h							
Death	0	0					
Pneumothorax requiring chest tube placement >7 d	1 (2)	1					
Hemoptysis >150 mL	0	0					
Invasive ventilation >24 h	0	0					
Total	1 (2)	1					
Composite score within 12 mo							
Death	4 (8)	4		3 (6)	3	2 (−8 to 12)	.99
Pneumothorax requiring chest tube placement >7 d	1 (2)	1		0	0	2 (−2 to 6)	.99
Hemoptysis >150 mL	0	0		0	0		
Invasive ventilation >24 h	1 (2)	1		3 (6)	3	−4 (−12 to 4)	.62
Pneumonia requiring hospitalization	9 (18)	11		2 (4)	2	14 (2 to 26)	.03
Lung transplantation	0	0		0	0		
Total	14 (28)	17		6 (12)	8	16 (1 to 31)	.046

[a] Data are shown as No. of events and No. of patients with at least 1 serious adverse event. Serious adverse events are stratified by occurrence within 30 days or between 30 days and 12 months after treatment. Two-sided tests were used for safety analyses.

[b] Difference between groups in the percentage of patients with events through 12 months.

[c] Recurrence of pneumothorax after a first pneumothorax within 1 month after procedure.

[d] The cause of death was peritonitis.

[e] The causes of death were chronic obstructive pulmonary disease exacerbation, mesenteric ischemia, and unknown.

[f] The causes of death were chronic obstructive pulmonary disease exacerbation in all 3 cases, associated with hepatitis in 1 case and associated with mesenteric ischemia in 1 case.

(95% CI, 1%-31%; *P* = .046). Within 12 months, 4 deaths (8%) occurred in the coil group and 3 deaths (6%) in the usual care group, with a difference between groups of 2% (95% CI, −8% to 12%; *P* = .99). The most frequent nonserious adverse event was mild self-resolving hemoptysis (< 5 mL) within 30 days after the procedure (48%).

Health Economic Evaluation

The health economic evaluation was based on data from all 50 patients in each group. At 1 year, the mean cost difference per patient was $47 908 (95% CI, $47 879-$48 073; *P* < .001) (**Table 4**). The change in mean QALYs at 1 year was 0.038 (95% CI, 0.038-0.040) in the coil group vs −0.023 (95% CI, −0.025 to −0.023) in the usual care group. The mean difference in QALYs between the 2 groups was 0.061 (95% CI, 0.061-0.064; *P* = .02). The 12-month incremental cost-effectiveness ratio was $782 598 per QALY (95% CI, $663 496-$1 327 212 per QALY). The uncertainty associated with the cost-effectiveness of coil treatment is shown as a scatter plot of the mean cost and QALY differences in eFigure 5A and the acceptability curve is shown in eFigure 5B in Supplement 2.

Discussion

To our knowledge, this is the first randomized multicenter study assessing the 6-month efficacy, 1-year safety, and cost-effectiveness of endobronchial coil treatment in severe emphysema. Among patients followed up for 6 months, bronchoscopic treatment with nitinol coils compared with usual care resulted in improved exercise capacity with high short-term costs. One of the main strength of this study is the completeness of follow-up at both 6 and 12 months. Coil treatment was associated with a significant decrease in lung hyperinflation and sustained improvement in quality of life. The magnitude of changes in lung function and quality of life were very similar

Table 4. Resource Utilization and Costs by Randomization Group Over a 12-Month Period

Resources	Coil Treatment (n = 50)	Usual Care (n = 50)	Difference (95% CI)	*P* Value[a]
Total length of stay, mean (SD), d				
First coil treatment	3.1 (1.6)	NA		
Second coil treatment	3.6 (2.5)	NA		
Patients with ≥1 rehospitalization, No. (%)	15 (30)[b]	9 (18)[b]	6	.16
No. of rehospitalizations per patient				
Mean (SD)	0.5 (1)	0.2 (0.5)	0.3 (0.3 to 0.3)	.21
Median (IQR)	0 (0-1)	0 (0-1)		
Hospital costs, mean (SD), US $[c]				
First coil treatment				
Medical devices	20 214 (1943)	NA		
Staff	598 (158)			
Operating room	560 (147)			
Hospital stays	2882 (3084)			
Median (IQR)	1399 (1399-3094)			
Second coil treatment				
Medical devices	18 395 (5061)	NA		
Staff	523 (191)			
Operating room	492 (178)			
Hospital stays	2883 (3053)			
Median (IQR)	1399 (1399-3094)			
Rehospitalization	1882 (4195)	910 (2675)	972 (952 to 1042)	.14
Median (IQR)	0 (0-1170)	0 (0-0)		
Consultation costs	1259 (1397)	1309 (1603)	−50 (−69 to −32)	.85
Median (IQR)	658 (403-1448)	601 (345-1561)		
Transportation costs	351 (420)	160 (251)	191 (191 to 210)	.01
Median (IQR)	211 (0-590)	0 (0-253)		
Home oxygen costs	2947 (2553)	2706 (2564)	241 (212 to 275)	.49
Monitoring tests	670 (95)	688 (48)	−19 (−21 to −19)	.29
Imaging	166 (27)	139 (9)	28 (28 to 28)	<.001
Total 1-y costs	53 821 (10 475)	5912 (3529)	47 908 (47 879 to 48 073)	<.001

Abbreviations: IQR, interquartile range; NA, not applicable.

[a] *P* values were derived from 2-sided *t* tests for equality of means.

[b] The total number of rehospitalizations was 26 among 15 patients with a mean length of hospital stay of 7.3 days (SD, 10.8 days) and a median of 4 (IQR, 1-9) in the coil group. The total number of rehospitalizations was 11 among 9 patients with a mean length of hospital stay of 3.5 days (SD, 3.8) and a median of 2 (IQR, 0-8) in the usual care group (2-sided *P* = .17 for the difference in length of stay between the coil and usual care groups).

[c] Costs are in 2014 US dollars; US $1 = €0.754 in purchasing power parity.

to results of uncontrolled studies assessing bilateral coil treatment[9-14] and to the results of a recent meta-analysis.[22] The changes in quality of life in our study were higher than usually observed in endobronchial lung volume reduction clinical trials.[3,4] Because our study was designed to mirror real-life clinical decision making, computed tomography assessments were conducted by each investigator without central reading center or proprietary software analyses. Collateral ventilation was not evaluated because fissure integrity did not influence response to coil treatment.[11] There was no difference in efficacy between heterogeneous and homogeneous emphysema, as previously shown.[9,22] To evaluate coils as a therapeutic option for patients typically excluded from lung volume reduction trials, we did not exclude patients with 6-minute walk test results of less than 140 m, diffusing capacity of the lungs for carbon monoxide of less than 20% predicted, lower lobe–predominant emphysema, homogeneous emphysema, hypoxemia, hypercapnia, or α_1-antitrypsin deficiency or patients taking anticoagulation drugs (except for vitamin K antagonists) or antiplatelet drugs with aspirin or clopidogrel. On the other hand, our inclusion criteria of an RV of greater than 220% predicted was more restrictive than in previous coil treatment studies.[22] Overall, our population was a unique severely hyperinflated and homogeneous emphysema population relative to other large lung volume reduction trials.

There were several limitations to this study. First, the prespecified statistical analysis for efficacy was 1-tailed. Based on this method, the trial met its prespecified primary end point for success at 6 months. However, additional larger studies with longer follow-up using 2-tailed statistical analyses are needed to draw a definitive conclusion regarding the long-term efficacy of coil treatment. Second, this study was neither sham controlled nor blinded, which needs to be considered for the interpretation of the 6-minute walk test, which is effort dependent. Third, the 6-minute walk test method was a single test with no supplemental oxygen, and the cutoff to define a responder was 54 m.[19] The lack of practice of a second 6-minute walk test has been shown to increase the variance of this measure.[23] The American Thoracic Society guidelines recommend a standard oxygen titration protocol to determine walk

oxygen prescription, which was used in other lung volume reduction randomized trials.[1-4] The 54-m cutoff is twice the most recent minimal clinically important difference standards for the 6-minute walk test, which are between 25 m and 30 m.[24] Finally, a key factor influencing our 6-minute walk test outcome may have been prebaseline pulmonary rehabilitation, which was an inclusion criterion in our study. In a recent meta-analysis, the mean change in the 6-minute walk test result after rehabilitation in chronic obstructive pulmonary disease was estimated to be 43.9 m.[25] Our study showed a relatively modest magnitude of change, with a between-group difference of 21 m in the 6-minute walk test at both 6 and 12 months, which was statistically significant at 6 months when analyzed as percent change but not when analyzed by change in distance walked and not significant at 12 months (although our study was not powered for a 12-month end point). Compared with the meta-analysis on coil treatments,[22] our 6-minute walk distance changes from baseline were much lower at both 6 and 12 months, whereas the changes in lung function and quality of life were in the same range. Finally, the absence of systematic prespecified continuation of rehabilitation after randomization could be regarded as an issue for the assessment of the long-term benefits of the intervention.

When the between-group differences in the secondary end points were compared with validated minimal clinically important differences in chronic obstructive pulmonary disease, the improvement in quality of life assessed by the St George's Respiratory Questionnaire was largely higher than 4 points[26] at both 6 and 12 months (means, −13.4 and −10.6 points, respectively) and the improvement in dyspnea assessed by the Transition Dyspnea Index was higher than 1 unit[27] at both 6 and 12 months (means, 1.6 and 1.1 units, respectively). The mean between-group differences in changes in RV at 6 and 12 months were both 7% and roughly reached the minimal clinically important difference, which is a change between 6.1% and 8.6%.[28] For FEV_1, the mean between-group differences were 0.09 L at 6 months and 0.08 L at 12 months and did not reach the minimal clinically important difference of 0.1 L.[29]

The magnitude and severity of serious and nonserious adverse events in this study were consistent with previous coil studies,[22] similar to endobronchial valves,[3,4] and far less than for lung volume reduction surgery.[1,2] The rate of pneumonia was very similar to that recently reported in a meta-analysis of 140 patients treated with coils.[22] All cases of pneumonia resolved with medical care. The mechanisms involved in pneumonia may result from local airway irritation, subsegmental airway closure, tension-induced inflammation, or local ischemia rather than from an infectious mechanism. Additional studies assessing pneumonia or lung opacities associated with coil treatment are needed to better understand the mechanisms, risk factors, and short-term and long-term evolution. Our study also demonstrated the feasibility of bilateral coil treatment in this severely ill population; 94% of patients assigned to the coil group completed bilateral treatment.

The study design included a health economic analysis to inform health care payers. The short duration of the follow-up precluded any robust conclusion on the long-term efficiency of the procedure because the procedure and device costs should be allocated over the total duration of clinical benefit. If we assumed that the QALYs gain could be maintained over at least 3 years with identical follow-up costs in both groups, the incremental cost-effectiveness ratio would decrease to about $270 000 per QALY, close to the incremental cost-effectiveness ratio reported for lung volume reduction surgery in the United States.[30] This cost-effectiveness ratio at 1 year and modeled to 3 years would not be considered efficient enough to warrant adopting the technology by most countries. Implementation of this technique in a large-scale emphysema population is likely to require this additional data given the high per-patient cost in the short run and the uncertain effect on total health care expenditures. Therefore, our study included both a crossover and an extended (5-year) follow-up including a health economic analysis of all treated patients.

Conclusions

In this preliminary study of patients with severe emphysema followed up for 6 months, bronchoscopic treatment with nitinol coils compared with usual care resulted in improved exercise capacity with high short-term costs. Further investigation is needed to assess durability of benefit and long-term cost implications.

ARTICLE INFORMATION

Author Affiliations: Service de Pneumologie, INSERM U903, Hôpital Universitaire de Reims, Reims, France (Deslée); Service de Pneumologie, Hôpital Universitaire Bichat, Paris, France (Mal, Marceau); Service d'Oncologie Thoracique, Maladies de la Plèvre, Pneumologie Interventionnelle, Hôpital Universitaire de Marseille, Marseille, France (Dutau, Laroumagne); Département de Pneumologie et Addictologie, PhyMedExp, Inserm U1046, CNRS UMR, Hôpital Universitaire de Montpellier, Montpellier, France (Bourdin, Mallet); Service de Pneumologie, Hôpital Universitaire de Saint-Étienne, Saint-Étienne, France (Vergnon); Clinique Universitaire de Pneumologie, Pôle Thorax et Vaisseaux, Inserm 1055, Hôpital Universitaire de Grenoble Alpes, Grenoble, France (Pison); Service de Pneumologie, Hôpital Universitaire de Strasbourg, Strasbourg, France (Kessler); Service de Pneumologie, Hôpital Universitaire d'Amiens, Amiens, France (Jounieaux); Service de Pneumologie, Hôpital Universitaire de Rouen, Rouen, France (Thiberville); Service de Pneumologie, IRCAN, UMR CNRS 7284/Inserm U1081, Team 3, Hôpital Universitaire de Nice Sophia Antipolis, Nice, France (Leroy, Marquette); Département de Pharmacovigilance, Hôpital Universitaire de Reims, Reims, France (Dukic); Département de Méthodologie, Pôle Recherche-Innovations, Hôpital Universitaire de Reims, Reims, France (Barbe, Jolly); URC Eco IdF, Unité de Recherche Clinique en Économie de la Santé d'Ile de France, AP-HP Paris, Paris, France (Bulsei, Durand-Zaleski).

Author Contributions: Dr Deslée had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Deslée, Barbe, Jolly, Durand-Zaleski, Marquette.
Acquisition, analysis, or interpretation of data: Deslée, Mal, Dutau, Bourdin, Vergnon, Pison, Kessler, Jounieaux, Thiberville, Leroy, Marceau, Laroumagne, Mallet, Dukic, Barbe, Bulsei, Durand-Zaleski, Marquette.
Drafting of the manuscript: Deslée, Barbe, Jolly, Durand-Zaleski, Marquette.
Critical revision of the manuscript for important intellectual content: Deslée, Mal, Dutau, Bourdin, Vergnon, Pison, Kessler, Jounieaux, Thiberville, Leroy, Marceau, Laroumagne, Mallet, Dukic, Bulsei, Durand-Zaleski, Marquette.
Statistical analysis: Barbe, Bulsei, Jolly, Durand-Zaleski.

Obtained funding: Deslée, Barbe, Jolly, Durand-Zaleski, Marquette.
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Study supervision: Deslée, Kessler, Jolly, Durand-Zaleski, Marquette.

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Group Information: The members of the REVOLENS Study Group include all authors and Hervé Vallerand, MD, Sandra Dury, MD, Jeanne Marie Perotin, MD, François Lebargy, MD, PhD (Hôpital Universitaire de Reims); Johanna Pradelli, MD, Matthieu Buscot, MD, Pierre Wolter, MD, Michel Poudenx, MD (Hôpital Universitaire de Nice); Marie Christine Dombret, MD, Frédérique Servin, MD, Marie Pierre Debray, MD, Cécile Chenivesse, MD (Hôpital Universitaire Bichat, Paris); Alain Palot, MD, Carine Gomez, MD, Philippe Astoul, MD (Hôpital Universitaire de Marseille); Nathalie Lesavre, MD (Centre d'Investigation Clinique 1409, AP-HM, Marseille); Anne Sophie Gamez, MD, Philippe Torodo, MD, Christophe Brousse, MD, Clément Broissin, MD (Hôpital Universitaire de Montpellier); Yoann Thibout, MD, Fabrice Di Palma, MD, Frédéric Costes, MD (Hôpital Universitaire de Saint-Etienne); Amandine Briault, MD, François Arbib, MD (Hôpital Universitaire de Grenoble); Michele Porzio, MD, Benjamin Renaud-Picard, MD (Hôpital Universitaire de Strasbourg); Bénédicte Toublanc, MD, Géraldine François, MD (Hôpital Universitaire d'Amiens); Antoine Cuvelier, MD, PhD, Samy Lachkar, MD (Hôpital Universitaire de Rouen); Margaux Verdier, Michael Maizieres, PhD, Delphine Gras, PhD (monitoring team, Hôpital Universitaire de Reims); Philippe Benoit, MD (Pharmacie, Hôpital Universitaire de Reims); Annick Leclainche (data manager, Hôpital Universitaire de Reims). Data and safety monitoring board: François Fourrier, MD, PhD, Eric Hachulla, MD, PhD, Nicolas Roche, MD, PhD, Daniel Dusser, MD, PhD.

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