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ORIGINAL RESEARCH

The Safety and Feasibility of Re-treating Patients with Severe Emphysema with Endobronchial Coils: A Pilot Study

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ABSTRACT

Severe emphysema patients who have been treated with endobronchial coils have been shown to initially benefit, but slowly decline in the years thereafter. Re-treating a patient with endobronchial coils could potentially lead to new improvements and may again reduce the rate of further decline. To our knowledge, until now, no results are published about patients who are re-treated. The primary aim of this study is to investigate the safety and feasibility of re-treating severe emphysema patients with endobronchial coils, using the PneumRx coil system. Furthermore, as secondary aim, we will evaluate the efficacy of re-treating these patients. Patients who at least 2 years ago were treated with endobronchial coils and responded clinically meaningful to this treatment were included in the study and re-treated. Safety was evaluated by the number of reported adverse events. Efficacy was evaluated 6 months after re-treatment, and measured by the change in quality of life, exercise capacity and pulmonary function testing. Eight patients were re-treated at a median of 1382 days (range 849–1545) after initial coil treatment with a median additional of 12 (10–15) coils per patient. During treatment, and until 6 months of follow-up, no unexpected adverse events occurred. Quality of life, exercise capacity and lung function did not change significantly 6 months after re-treatment. The results of this pilot study suggest that re-treating patients with endobronchial coils is feasible and safe. However, larger studies are needed to confirm these results and to investigate the efficacy and thus the clinical relevance.

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Introduction

In the past decade, the endobronchial coil treatment, a minor invasive bronchoscopic lung volume reduction treatment option for patients with severe emphysema was developed and investigated (1–4). The endobronchial coil is designed to compress the areas of lung parenchyma most damaged by emphysema. This compression reduces airflow to the treated portions of the lung, allowing enhanced airflow to healthier untreated portions of the lung (5). This technique is an alternative for patients who do not qualify for treatment with one-way endobronchial valves due to the presence of collateral ventilation, or lung volume reduction surgery due to a homogeneous emphysema distribution or comorbidities (6,7).

The combined data of four studies performed in Europe investigating the endobronchial coil treatment showed statistically significant improvements in pulmonary function, exercise capacity and quality of life at both 6 months and 12 months post treatment (1). Furthermore, a recently published randomized controlled trial showed statistically significant differences between the treatment group and control group 12 months post treatment in exercise capacity, lung function and quality of life parameters (2).

Recently, we published the results of our single-center long-term follow-up analysis, showing that the initial improvements in pulmonary function, exercise capacity and quality of life are slowly decreasing in the 2 years following the first treatment with the endobronchial coil system (8). This decline could be caused by natural decline due to ageing and disease progression, but could also be caused by a diminishing effect of the treatment. Re-treating the patient with endobronchial coils in other parts of the lung could potentially lead to new improvements in lung function, dyspnoea, exercise capacity and quality of life and may reduce the rate of decline.

To our knowledge, until now, no results are published about patients who are re-treated with the endobronchial coil system. Therefore, the aim of this study is to investigate the safety and feasibility of re-treating patients with severe emphysema with the endobronchial coil system. Furthermore, we will evaluate the efficacy of re-treating these patients.

Methods

Study population

Between April 2009 and September 2012, 49 patients were treated with the endobronchial coil system at our hospital in

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1 of 3 pilot studies (NCT01220908 (9), NCT01328899 (10) and NCT01421082 (11)). After completing these studies, patients were invited for a yearly voluntary follow-up visit to our hospital, and patients who indicated that they would like additional treatment could participate in this 'RECOIL' trial (NCT02012673). Patients could only be included in this trial when the initial coil treatment was at least 24 months ago and had a significant improvement in either 6-minute walk distance, FEV_1 or SGRQ score at 6 months after the initial treatment. The complete list of inclusion and exclusion criteria can be found in the online supplement (S1). The study was approved by the ethics committee of the University Medical Center Groningen, and all patients provided written informed consent.

Endobronchial coil treatment

The performed endobronchial coil treatment has been described before in detail (5,9). Based on the position of the already placed coils in the past and a new high-resolution chest CT (HRCT) scan, the pulmonary physician decided at which location in the lung, the additional coils were placed. The coils were placed by bronchoscope in one procedure under general anaesthesia.

Study design and measurements

Patients were reviewed and tested in the outpatient clinics at baseline and 6 months following the procedure. Safety was evaluated by reporting all adverse events until 6 months of follow-up. The following measurements were performed at the two visits. Pulmonary function was measured by spirometry and body plethysmography (Jaeger MasterScreen^{TM}, CareFusion, Germany) according to the ATS/ERS guidelines (12,13). Exercise capacity was measured by a 6-minute walk distance test according to the ATS guidelines (14). Quality of life was measured by the St. George's Respiratory Questionnaire (SGRQ) (15) and Clinical COPD Questionnaire (CCQ) (16). Dyspnoea severity was measured by the modified Medical Research Council scale (mMRC) score (17).

Statistical analyses

Safety will be evaluated descriptively. To evaluate the efficacy of re-treating patients with the endobronchial coil system, non-parametric statistics will be performed due to the low number of patients. Descriptive statistics will be presented as median (range). To compare the difference in efficacy parameters between baseline and 6-month follow-up, a Wilcoxon signed-rank test will be performed. p-values below 0.05 are considered statistically significant. Statistical analyses were performed using IMB SPSS Statistics version 22.

Results

Study population and procedure characteristics

In total, 8 patients participated in this pilot study between January 2014 and February 2016. Patient characteristics are shown in Table 1. Procedure characteristics per patient are shown in Table 2. Patients were re-treated after a median of 1382 days (approximately 3 year and 10 months; range: 849–1545 days) after the initial treatment. All treatments were executed according to the treatment plan. The median procedure time was 24.5 minutes (range 12–32), and the median number of coils placed was 12 (range 10–15). Figure 1 shows the chest X-ray of one example patient after the initial treatment and after the re-treatment with coils. Median hospital stay was 1 night (range 1–4) after the procedure.

Table 1. Patient characteristics (n = 8).

Female/Male, n	5/3
Age, years	65.5 (52–74)
Pack-years, years	30.5 (8–45)
StO_2, %	95 (87–97)
$PaCO_2$, kpa	5.7 (5.18–6.68)
PaO_2, kpa	9.67 (8.75–10.96)
SGRQ symptoms, score	39.2 (8.9–93.6)
SGRQ activity, score	89.2 (47.2–93.3)
SGRQ impact, score	38.9 (15.9–54.3)
SGRQ total, score	54.5 (29.1–70.2)
CCQ total, score	2.9 (1.4–3.3)
mMRC, score	3 (2–3)
6MWD, meter	342 (138–495)
FEV_1, %pred	21.5 (13–26)
FVC, %pred	69.0 (48–89)
RV, %pred	255 (200–375)

Data are presented as n(%) or median (range).
StO_2, Transcutaneous oxygen saturation measured at room air, $PaCO_2$:arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; SGRQ, St. George's Respiratory Questionnaire; CCQ, Clinical COPD Questionnaire; mMRC, modified Medical Research Council scale; 6MWD, 6-minute walk distance; FEV_1, Forced expiratory volume in 1-second; FVC, Forced Vital Capacity; RV, Residual Volume.

Safety

Table 3 shows the reported serious and non-serious adverse events. During the study, no death, respiratory failure, pneumothorax or severe haemoptysis occurred. Within the first month after the treatment, 1 patient had a COPD exacerbation that required hospitalization. Furthermore, 1 patient had a coil associated opacity reaction, 1 patient experienced increased dyspnoea and 2 patients chest pain (non-cardiac) resolving with medication. Between 1-month and 6-month follow-up, 2 patients were hospitalized for a COPD exacerbation and 1 patient for a pneumonia. Furthermore, 1 patient had a COPD exacerbation resolving with medication. None of the occurred serious adverse events were deemed to be directly related to the device or procedure.

Efficacy

No significant improvements were found 6 months after the re-treatment in quality of life, exercise capacity or pulmonary function parameters (all $p > 0.05$, Table 4). Figure 2 shows the change in quality of life, exercise capacity and pulmonary function before and after the initial treatment and after the re-treatment with endobronchial coils. Individual patient data are shown in Figure S2 in the online supplement.

Discussion

To our knowledge, until now, this is the first study that publishes results of re-treating patients with endobronchial

Table 2. Procedure characteristics per patient.

Patient	Initial target	Days after initial target	Re-coil target	Number of coils	Procedure time (min)	Hospital admission days
1	RUL + RLL	1545	LUL + LLL	15	27	3
2	LUL + LLL+RUL	1349	LLL	10	19	1
3	RUL + LUL	1437	LUL + LLL	12	12	1
4	RUL + RLL	1475	LUL + LLL	15	27	1
5	RUL + LUL	1309	LLL	12	32	4
6	RUL + LUL	849	LLL	11	26	1
7	RUL + LUL	1405	RLL	12	15	1
8	RUL + LUL	1358	RLL	14	23	1

RUL, Right upper lobe; RLL, Right lower lobe; LUL, Left upper lobe; LLL, Left lower lobe.

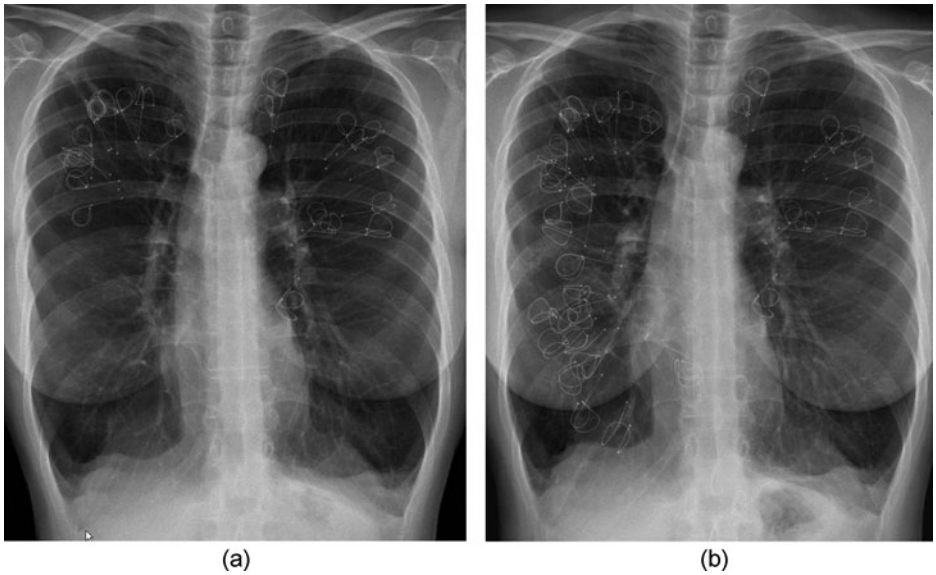

Figure 1. Chest X-ray of 1 example patient after the initial treatment and after the re-treatment with coils. Panel (1a) Chest X-ray after initial treatment. Panel (1b) Chest X-ray after re-treatment with coils.

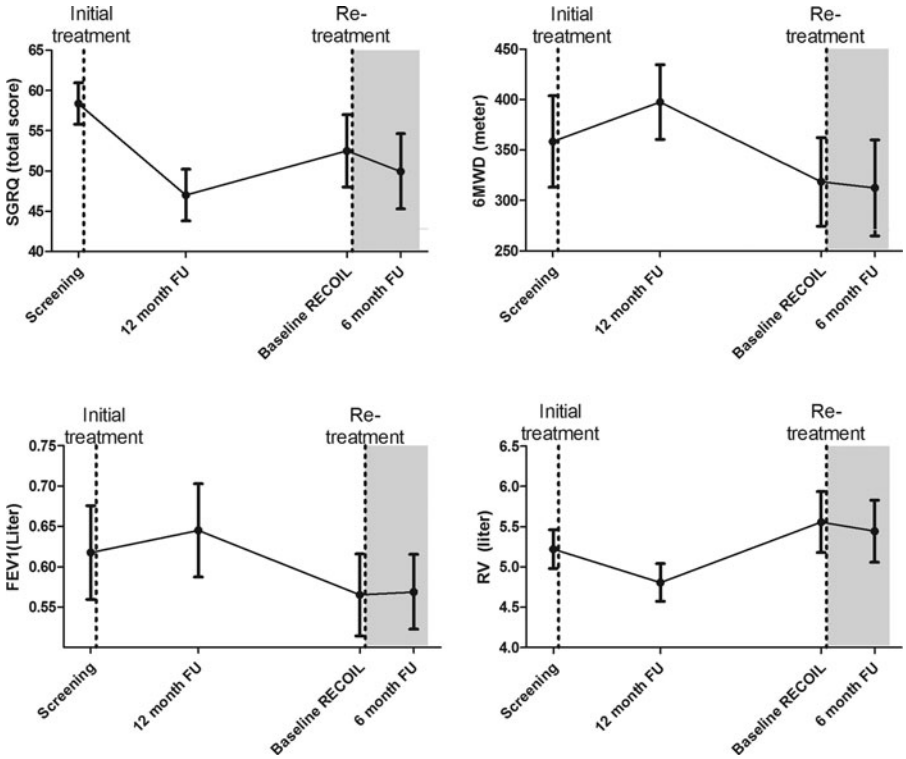

Figure 2. Change in quality of life, exercise capacity and lung function (n = 8) Data are presented as mean and standard error of the mean (error-bars). The baseline of the RECOIL study was 1382 days (range 849–1545 days) after the initial treatment.

Table 3. Number of reported (serious) adverse events.

Serious adverse events	<30 days after treatment	Between 30 and 180 days after treatment
Death	0	0
Respiratory failure	0	0
COPD exacerbation requiring hospitalization	1	2
Pneumonia	0	1
Pneumothorax	0	0
Hemoptysis	0	0
Adverse events		
Coil associated opacity reaction	0	1
Dyspnea	1	0
Influenza	1	0
COPD exacerbation	2	1
Chest pain	2	0

Data are presented as number of adverse events reported.

coils. Our results show that it is feasible to re-treat patients with endobronchial coils system approximately 3 years after the initial treatment. Furthermore, even in this very diseased patient group, no unexpected serious or non-serious adverse events occurred within 6 months after treatment. In this small group, no significant changes in efficacy parameters were found 6 months after the treatment.

Our results suggest that it is feasible to re-treat patients with the endobronchial coils system approximately 3 years after the initial treatment. All individual treatment plans based on the HRCT scan and previous treatment with the endobronchial coil system were executed without problems. However, it should be further investigated how the additional coil treatment procedure can be optimized. For example, we choose to include patients who were treated with coils at least 2 years ago. Our longitudinal pilot study showed that the treatment with coils was beneficial for a large group of patients after 1 year, with after 3-year overall clinical parameters returning to baseline (8). It is questionable whether it is better to add coils earlier when the decline starts or later when the benefit is diminished completely. Furthermore, in this study, a total of 10–15 additional coils were placed in 1 procedure. In the initial treatment, 6 patients who were treated bilaterally received 19–24 coils in 2 lungs and 2 patients who were treated unilaterally received 15 coils in 1 lung. Perhaps, it can be speculated that the number of additional coils placed was not sufficient to obtain optimal clinical benefit.

During hospitalization, between hospitalization and 1 and 6 months after treatment, no unexpected adverse events occurred. These results suggest that it is safe to re-treat patients with the endobronchial coils system. However, the limited number of patients precludes drawing firm conclusions regarding safety of re-treatment. The type of adverse events were comparable with other trials investigating the endobronchial coil treatment (1,2). Furthermore, the frequency of the occurrence of the adverse events in this trial was lower compared to the other trials, but also the sample size was lower and the trial was only performed at 1 hospital.

Table 4. Changes in efficacy parameters 6 months after treatment (n = 8).

	Baseline Re-Coil	6 Months FU	*p*-value
SGRQ, total score	54.5	53.9	0.327
CCQ, total score	2.9	2.7	0.497
mMRC, score	3.00	2.5	0.317
6MWD, meter	342	353	0.624
FEV_1, liter	0.53	0.53	0.566
FVC, liter	2.27	2.28	0.161
RV, liter	5.17	5.14	0.575

Data are presented as median. Difference between baseline and 6 months follow-up was analyzed with a Wilxocon signed rank test.

FU, Follow-up; SGRQ, St. George's Respiratory Questionnaire; CCQ, Clinical COPD Questionnaire; mMRC, modified Medical Research Council scale; 6MWD, 6-minute walk distance; FEV_1, Forced expiratory volume in 1-second; FVC, Forced Vital Capacity; RV, Residual Volume.

We found earlier that the rate of decline in these patients in terms of FEV_1 did not change after the treatment with endobronchial coils (8), which was also found after lung volume reduction surgery (LVRS) (18,19). Emphysema is characterized by gradual destruction and disappearance of alveolar walls, which probably also continue after the treatment with coils. The coil is designed to compress the areas of lung parenchyma most damaged by emphysema, and placing additional coils could target the lung parenchyma areas, which show on-going destruction. In this pilot study, the additional coils were placed in a different target lobe than the initial treatment, while it also would be interesting to investigate whether treatment in the same target lobe is feasible and effective. However, with already coils being present in all subsegments of the already treated lobes, this might be challenging.

Re-treating patients with endobronchial coils is only clinical relevant when patients benefit from this additional treatment. The subjects included in this pilot study responded before to the coil treatment and had an initial residual volume of 255% of predicted and were therefore likely to benefit from re-treatment (2). However, our results showed no significant improvement in quality of life, dyspnoea severity, exercise capacity and lung function 6 months after the re-treatment. On the other hand, also no worsening of these parameters was observed after the re-treatment with endobronchial coils. However, the number of patients in this trial is too low to draw definitive conclusions about efficacy; thus, a larger trial is needed to investigate whether patients will benefit from re-treatment with endobronchial coils or not. Unfortunately, there are only limited alternative treatment options for this group of patients. The patients in this trial could not be treated with endobronchial valves because of the presence of collateral ventilation and due to the main homogeneous distribution of the emphysema, LVRS was neither an option (20). Lung transplantation could be an option, but this treatment is only available for a very selective group of severe emphysema patients with limited co-morbidity.

The main disadvantage of this study was the low number of patients. The main aim of this pilot study was to investigate whether it is feasible and safe to re-treat patients with endobronchial coils more than 2 years after the initial treatment. The results suggest that re-treating is feasible and safe but a larger multicentre study is necessary to confirm these results. Furthermore, our patients were one of the first ones ever treated with endobronchial coils in pilot studies, which may have biased the results.

In conclusion, the results of this pilot study suggest that it is feasible and safe to re-treat patients with endobronchial coils approximately 3 years after the initial coil treatment. In this small group of patients, little or no benefit was found of the

re-treatment with coils. However, larger studies are needed to confirm these results and to investigate the efficacy and thus the clinical relevance of re-treating patients.

Role of the sponsors

PneumRx funded the original pilot studies but had no involvement of any kind in this study.

Declaration of interest

JH and NtH declare no conflicts of interest. KK received travel grants from PneumRx and financial support from PneumRx as a consultant not related to this study. DJS is a physician advisor to PneumRx and received travel grants and speakers fees for presentations at scientific and educational meetings from PneumRx.

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