Review Article

Lung volume reduction with endobronchial coils for patients with emphysema

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Abstract: The lung volume reduction coil treatment is a minimally invasive bronchoscopic treatment option for emphysema patients who suffer from severe hyperinflation. The treatment is aimed at a large group of patients where lung volume reduction surgery and bronchoscopic lung volume reduction using endobronchial valves are no option, or alternatively, can be offered as a bridge to lung transplantation. The nitinol coil exhibits a shape memory effect and is biologically inert. The lung volume reduction coil procedure is performed in two separate treatment sessions, targeting one lobe per session, with the contralateral lobe being treated 4 to 8 weeks after the first session. In one treatment session, around 10 to 14 coils, thereby treating an entire lobe, are being placed. Selecting optimally treated, symptomatic chronic obstructive pulmonary disease (COPD) patients with emphysema and severe hyperinflation, while avoiding significant airway disease such as asthma, chronic bronchitis and bronchiectasis, is key to achieve treatment success. Three randomized clinical trials investigating lung volume reduction coil treatment have been published until now, reporting the results of 452 treated patients up to 12 months after coil treatment. Lung volume reduction coil treatment results in significant improvement of pulmonary function outcomes and quality of life in patients with severe hyperinflation. The most common complications of lung volume reduction coil treatment are: COPD exacerbations, pneumonia, Coil Associated Opacity and an increased risk of pneumothorax. The purpose of this article is to describe the coil technique and review the available literature regarding effect, safety and future perspectives of lung volume reduction with coils for emphysema patients.

Keywords: Lung volume reduction; bronchoscopy; chronic obstructive pulmonary disease (COPD); coils; emphysema

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Background

Emphysema is characterized by lung parenchymal destruction caused by tobacco smoking, inhalation of other toxic agents, together with predisposed genetic host factors such as α_1-antitrypsin deficiency (1). Lung parenchymal tissue destruction in severe emphysema is associated with increased lung elasticity, loss of elastic recoil, expiratory airway collapse, leading to static as well as dynamic hyperinflation and causing a significant reduction of lung function, exercise capacity and quality of life.

For patients with severe emphysema, the current available treatment options are: smoking cessation, bronchodilators, anti-inflammatory agents, vaccinations, proper nutrition, pulmonary rehabilitation, the use of oxygen, chronic non-invasive ventilatory support and surgical interventions like

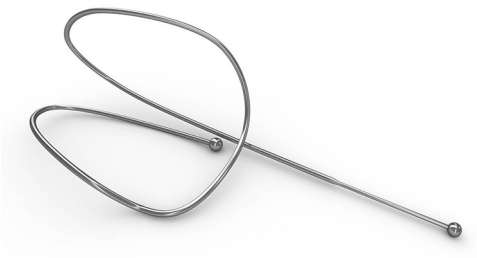

Figure 1 RePneu Coil (125 mm); used with permission of PneumRx/BTG.

lung volume reduction surgery and lung transplantation. Despite all these available treatment options, the majority of patients still remains highly symptomatic or do not qualify for surgical techniques.

Several minimal invasive bronchoscopic treatment options for severe emphysema have emerged, such as endobronchial valves (2), lung volume reduction coils (3) and more experimental techniques such as bronchoscopic thermal vapor ablation (4) and biological lung volume reduction (Aeriseal lung sealant) treatment (5), all aiming at reducing hyperinflation (6). Also very new airway directed treatments such as targeted lung denervation (7) and metered liquid nitrogen cryospray (8) are in development. Hyperinflation is known to play a key role in the feelings of dyspnea and reduced exercise capacity in emphysema (9,10). Targeting this hyperinflation component might significantly relief dyspnea and increase quality of life and exercise performance (2,11).

Depending on appropriate patient selection and correct placement, endobronchial valves reduce hyperinflation which manifests in clinical improvement (12). Responders to valve therapy are only patients with absence of interlobar collateral flow (assessed by quantitative CT fissure analysis, and/or the CHARTIS® catheter system) between the target lobe and adjacent lobe (2,13,14).

For patients with presence of interlobar collateral ventilation, of which prevalence is estimated to be around 60% in severe emphysema (15), coils might be a potential treatment option (16).

Lung volume reduction with coils

The coil

The RePneu® coil treatment (RePneu® coil system, PneumRx Inc./BTG, Santa Clara, CA, USA) is a bronchoscopic therapy for the treatment of patients with severe emphysema. The coil consists of a nickel-titanium alloy (nitinol) which exhibits a shape memory effect and is biologically inert (*Figure 1*). The first application in humans was performed in 2008 after extensive testing of the treatment in animal models (17). The coil is produced in three different sizes (100/125/150 mm) to accommodate different airway lengths.

Treatment procedure

The procedure is preferably performed with the patient undergoing general anesthesia, using a 9 mm flexible endotracheal tube with pressure controlled ventilation at a low ventilation frequency (~10/min) with an inspiratory/expiratory ratio of about 1:4 to allow sufficient expiration in these severely air-trapped patients. Normally, patients remain hospitalized one night for regular observation after treatment. All our patients receive both corticosteroids (prednisolone 30 mg per day), from the pre-treatment day up to 5 days after treatment, as well as antibiotic prophylaxis (azithromycin 250 mg per day) starting on the treatment day up to 30 days post treatment (expert opinion).

The coil placement procedure is, for safety reasons, performed in two separate treatment sessions, targeting one lobe per session, the contralateral lobe being treated 4 to 8 weeks after the first session. Bilateral treatment is necessary to achieve optimal treatment benefit (3). The most diseased lobes should be treated, identified using quantitative CT analysis and when needed perfusion scanning as guidance. Coil placement is performed using a bronchoscope with a therapeutic size working channel (2.8 mm internal diameter or larger). It is recommended to take a routine microbacterial culture sample during the first inspection of the bronchial tree, this to be optimally informed about airway colonization, with respect to potential future infectious events.

The coils are delivered, bronchoscopically, into the segmental and subsegmental airways using a special catheter delivery system. Placement is performed under fluoroscopy to visualize positioning and coil sizing (*Figure 2*). The procedure starts with a guidewire, bearing fluoroscopic markers, that is used to measure airway length and to position the coil at a fair distance from the pleura (to avoid pneumothorax and pleural pain). When the guidewire is in the correct position, a delivery catheter can be advanced over the guidewire. The coils are situated in this delivery

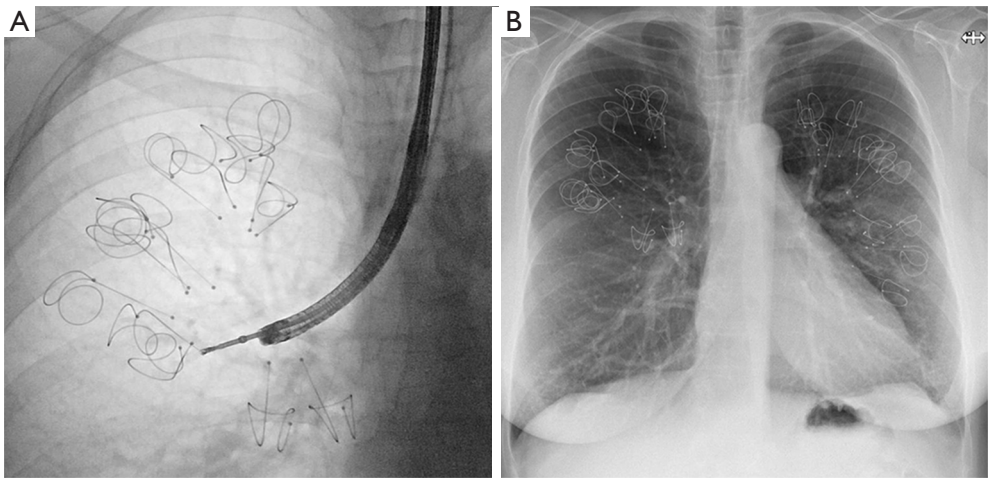

Figure 2 Coil treatment radiological imaging. (A) Fluoroscopic image during coil treatment of the right upper lobe in a severe emphysema patient; (B) chest X-ray after treatment with coils.

catheter in a straight configuration. When the target treatment area is reached, the delivery catheter is pulled back and the coil reverts to its non-straightened coil shape, resulting in a compression of the local lung parenchyma. The coil can then subsequently be released.

In one treatment session, around 10 to 12 coils for upper lobes and 10 to 14 coils for lower lobes are being placed in the desired lobe. During the procedure the coils can be removed and repositioned. The coil treatment is regarded permanent. However, when for example persistent thoracic pain requires removal of one coil, this has been shown feasible up to 10 months after implantation in specialist centers (18).

Mechanism of action

The hypothesized mechanism of action of the coil treatment is that the compression of the lung parenchyma by the coils results in less hyperinflation and simultaneously better transmits the elastic recoil pressure, meaning a real lung volume reduction effect (19). Secondly, the coils reduce airflow towards the targeted segments of the lung and this consequently results in a redistribution of airflow towards healthier parts of the lung (20). Furthermore, a decrease in airway resistance occurs in the treated lobes (19,21). Finally, the volume reduction of the emphysematous treated areas could improve lung compliance and put the diaphragm in a better condition of function with, as a consequence, an increase in driving pressure of the expiratory flows (19,22,23).

Feasibility & efficacy

An overview of all published original coil studies is presented in *Table 1*.

The first pilot study on coil treatment started in 2008 in Heidelberg (Germany). Eleven patients were treated with up to 6 coils per lobe, demonstrating both feasibility and safety, but no statement on efficacy could be made (17).

The second pilot study started in 2009 in Groningen (The Netherlands). Sixteen patients were treated, demonstrating safety, feasibility and efficacy of the procedure by using the second generation of the coil and increasing the number of coils per treated lobe to 10–12. At 6-month follow-up after the final treatment, there were significant improvements of −14.9 points (P<0.001) in St. George's Respiratory Questionnaire (SGRQ), −11.4% (P<0.001) in residual volume (RV), +84.4 meter (P<0.001) in 6-minute walking distance (6MWD) and +14.9% (P=0.004) in forced expiratory volume in 1 second (FEV_1), compared to baseline (24).

The third study and first randomized controlled trial investigating coils was the RESET trial (Endobronchial coils for the treatment of severe emphysema with hyperinflation). Forty-six patients with both homogeneous and heterogeneous emphysema were allocated in a one-to-one ratio to either coil treatment (treatment group) or best medical care (control group). Patients were treated in two sessions, with the contralateral lobe being treated 1 month after the initial treatment. Outcome measures were performed 90 days after the final treatment or the

Table 1 Literature overview of original trials on the lung volume reduction coil treatment for emphysema

Author (publication year)	Title	Patients	Study design	NCT identifier
Herth *et al.* [2010]	Bronchoscopic lung volume reduction with a dedicated coil: a clinical pilot study	11	Pilot Study	N/A
Slebos *et al.* [2012]	Bronchoscopic lung volume reduction coil treatment of patients with severe heterogeneous emphysema	16	Pilot Study	NCT01220908
Shah *et al.* [2013]	Endobronchial coils for the treatment of severe emphysema with hyperinflation: a randomised controlled trial (RESET)	46	RCT	NCT01334307
Deslée *et al.*[2014]	Lung volume reduction coil treatment for patients with severe emphysema: a European multicentre trial	60	Feasibility Study	NCT01328899
Kontogianni *et al.* [2014]	Effectiveness of endobronchial coil treatment for lung volume reduction in patients with severe heterogeneous emphysema and bilateral incomplete fissures: a six-month follow-up	26	Retrospective Analysis	N/A
Klooster *et al.*[2014]	Lung volume reduction coil treatment in COPD patients with homogeneous emphysema: a prospective feasibility trial	10	Feasibility Study	NCT01421082
Hartman *et al.* [2014]	Long-term follow-up after bronchoscopic lung volume reduction treatment with coils in patients with severe emphysema	38	Retrospective Analysis	N/A
Zoumot *et al.* [2015]	Endobronchial coils for severe emphysema are effective up to 12 months following treatment: medium term and cross-over results from a randomised controlled trial	45	Retrospective Analysis	NCT01334307
Deslée *et al.* [2016]	Lung volume reduction coil treatment *vs.* usual care in patients with severe emphysema (REVOLENS)	91	RCT	NCT01822795
Sciurba *et al.* [2016]	Effect of endobronchial coils *vs.* usual care on exercise tolerance in patients with severe emphysema: the RENEW randomized clinical trial	315	RCT	NCT01608490
Hartman *et al.* [2017]	The safety and feasibility of re-treating patients with severe emphysema with endobronchial coils: a pilot study	8	Pilot Study	NCT02012673
Kontogianni *et al.* [2017]	Coil therapy for patients with severe emphysema and bilateral incomplete fissures—effectiveness and complications after 1-year follow-up: a single-center experience	86	Retrospective Analysis	N/A

N/A, not applicable; NCT, National Clinical Trial Register; RCT, randomized clinical trial.

equivalent visit for the usual care group. Differences between treatment and best medical care group scores in change from baseline were –8.4 points (P=0.04) in SGRQ, –0.31 L (P=0.03) in RV, +63.6 meter (P<0.001) in 6MWD and +10.6% (P=0.03) in FEV_1 at 90 days follow-up after the final treatment (25).

The fourth study, an open label feasibility study, investigating coils in strict homogeneous emphysema, confirmed the efficacy of treatment for this phenotype. At 6 months follow-up after treatment, there were significant improvements of –15 points (P=0.028) in SGRQ, –0.6 L (P=0.007) in RV, +61 meter (P=0.005) in 6MWD and +18.9% (not significant, P=0.102) in FEV_1, compared to baseline (21).

The fifth study, a European open-label feasibility study including 60 patients, confirmed the previously published single center results in a multicenter design with a good safety profile and sustained results up to 12 months follow-up. At 12 months follow-up after treatment, there were significant improvements of –11.1 points (P<0.001) in

Table 2 Efficacy outcomes of the main lung volume reduction coil treatment studies

Study	Slebos 2015 (meta analysis)[a]		Shah 2013 (RESET)	Deslée 2016 (REVOLENS)	Sciurba 2016 (RENEW)
Follow-up (months)	6	12	3	12	12
N	125	96	T23:C23	T44:C47	T158:C157
ΔFEV_1 (liters) (% relative change)	+10.4%[b]	+10.4%[b]	+10.6 (1.1 to 20.1)	+11 (5.2 to ∞)	+7.0 (97.5% CI: 3.4 to ∞)
ΔRV (liters)	−0.51±0.85	−0.43±0.72	−0.31(−0.59 to −0.04)	−0.36 (−∞ to −0.10)	−0.31 (97.5% CI: −∞ to −0.11)
Δ6MWD (meters)	+44.1±69.8	+38.1±71.9	+63.6 (32.6 to 94.5)	+21 (−5 to ∞), P=0.12	+14.6 (97.5% CI: 0.4 to ∞)
ΔSGRQ (units)	−9.5±14.3	−7.7±14.2	−8.4 (−16.2 to −0.47)	−10.6 (−∞ to −5.8)	−8.9 (97.5% CI: −∞ to −6.3)

95% CI unless otherwise indicated. P<0.05 unless otherwise indicated. [a], Slebos, 2012; Klooster 2014; Deslée 2014; Zoumot 2015; [b], % relative change in FEV_1 was calculated because only baseline and change scores were provided in the manuscript. T, treatment group; C, control group; Δ, change between baseline and follow-up; SD, standard deviation; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; RV, residual volume; 6MWD, 6-minute walking distance; SGRQ, St. George's Respiratory Questionnaire.

SGRQ, −0.71 L (P<0.001) in RV, +51.4 meter (P=0.003) in 6MWD and 0.11 L (P=0.037) increase in FEV_1, compared to baseline (26).

The sixth study and second randomized controlled trial was the REVOLENS trial (Lung Volume Reduction Coil Treatment *vs.* Usual Care in Patients with Severe Emphysema). One hundred patients were allocated in a one-to-one ratio to either coil treatment or usual care. Contralateral treatment took place 1 to 3 months after the first. Approximately 10 coils per targeted lobe were delivered. All patients were assessed at baseline and at 1, 3, 6 and 12 months after baseline. Differences between treatment and usual care group scores in change from baseline were −13.4 points (P<0.001) in SGRQ, −0.37 L (P=0.01) in RV, +21 meter (not significant, P=0.06) in 6MWD and +11% (P=0.01) in FEV_1 at 6 months post treatment (27).

The seventh study and third randomized controlled trial was the RENEW trial (Effect of Endobronchial Coils *vs.* Usual Care on Exercise Tolerance in Patients with Severe Emphysema), including 315 patients. Differences between treatment and usual care group scores in change from baseline were −8.9 points (P<0.001) in SGRQ, −0.31 L (P=0.01) in RV, +14.6 meter (P=0.02) in 6MWD and +7% (P<0.01) adjusted median increase in FEV_1 at 12 months post treatment. The greatest improvements occurred in the RV ≥225% predicted subgroups, in both heterogeneous and homogeneous emphysema phenotypes, highlighting the importance of the presence of hyperinflation (11).

An overview of efficacy outcomes of the larger studies is provided in *Table 2*.

Safety-profile

The most common complications of coil treatment are: chronic obstructive pulmonary disease (COPD) exacerbations, pneumonia, Coil Associated Opacity and an increased risk of pneumothorax (11,25,27).

In a 2015 meta-analysis, including 140 patients, no serious adverse events occurred periprocedural in any of the 259 coil procedures and no deaths or respiratory failures were reported. A total of 37 severe COPD exacerbations and 27 pneumonias requiring hospitalization were recorded among all patients up to 1 year of follow-up. Pneumothorax occurrence for which chest tube insertion was required was 6.4% per patient treated. Severe COPD exacerbation incidence was 3.1% in the first month after treatment, 2.9% per month from 1 to 6 months after treatment and 2.3% per month from 6 months up to 1 year follow-up. Pneumonia incidence was 3.5% per month during the first month after treatment, 1% from 1 to 6 months after treatment and 2.1% per month from 6 months up to 1 year follow-up (3).

Coil Associated Opacity, a phenomenon first described by the "RENEW" study investigators, is a noninfectious, localized tissue response that occurs post-coil implantation in approximately 5–10% of cases. Coil Associated Opacity is hypothesized to be induced by stress forces from the coils on lung parenchyma. Patients with Coil Associated Opacity can demonstrate symptoms comparable to infectious pneumonia and this makes it difficult to distinguish between them. A chest radiograph of a patient with Coil Associated Opacity is provided in *Figure 3*. Patients with Coil Associated Opacity exhibited superior 12-month

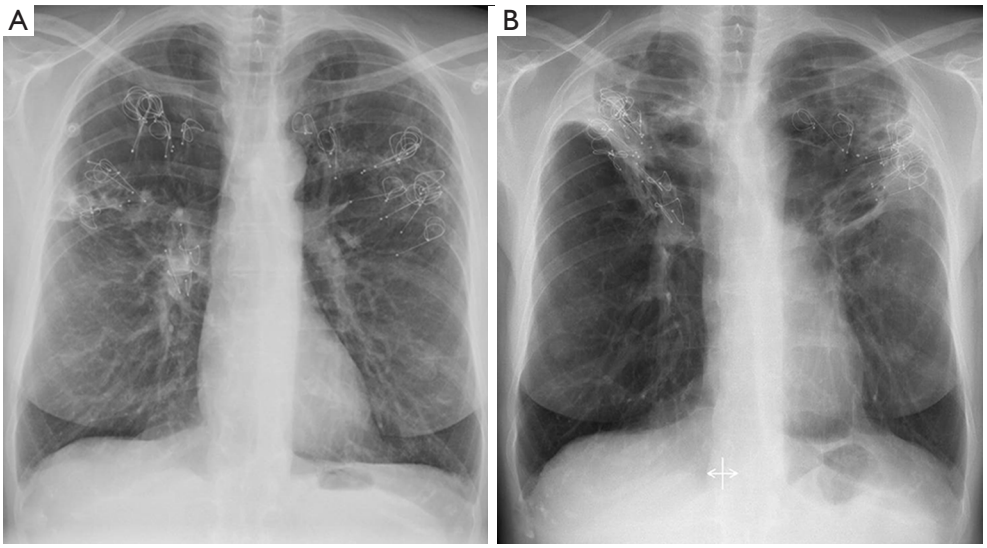

Figure 3 Coil Associated Opacity. (A) Post-treatment chest X-ray displaying a mild consolidation around the coil position ("Coil Associated Opacity") in the right lung; (B) chest X-ray 12 months post-treatment in the same patient showing significant volume reduction in both upper lobes due to a post inflammatory fibrotic crowding reaction of the coils resulting in a beneficiary outcome.

effectiveness outcomes compared to patients without Coil Associated Opacity or pneumonia (11).

Patient selection criteria

Coils are a potential treatment option for patients who do not qualify for endobronchial valve treatment [due to for example positive interlobar collateral ventilation status (16)] or lung volume reduction surgery, and can also be offered as a bridge to lung transplantation. Selecting optimally treated, symptomatic COPD patients with emphysema and severe hyperinflation (absolute minimal criteria for hyperinflation: RV >200% predicted and RV/TLC ratio >58%, measured using body plethysmography), while avoiding significant airway disease such as asthma, chronic bronchitis and bronchiectasis, is key to achieve treatment success (12,28,29). Additional patient inclusion and exclusion criteria specific for the coil treatment from our center are summarized in *Table 3*.

Long term follow-up & re-treatment with coils

To date, not a lot of data exists on longer term outcome after coil treatment. One single center study investigated the safety and efficacy of the coil treatment in the long term at 1, 2 and 3 years follow-up. At 3-year follow-up, no long-term unexpected adverse and device-related events occurred, with clinical benefit gradually declining over time (30).

Re-treatment with coils has been investigated in one pilot study, including eight patients. Re-treatment was performed at a median of 1,382 days after initial coil treatment with a median additional of 12 coils per patient. The trail was not powered for efficacy outcomes. No unexpected adverse events occurred, suggesting feasibility and safety of re-treatment (31).

Cost-effectiveness

Cost-effectiveness of the coil treatment has been investigated in the REVOLENS trial. Cost was estimated at $47,908 per patient above usual care at 1 year and the incremental cost-effectiveness ratio was $782,598 per additional quality-adjusted life-year. However, the short duration of the follow-up prevented the authors from drawing a conclusion on long term cost-effectiveness, as the financial costs of procedure and devices should be allocated over the total duration of clinical benefit. Possibly, the expected 5-year follow-up data from this clinical trial will provide more insight in cost-effectiveness of the coil treatment (27).

Conclusions and future perspectives

Three randomized clinical trials investigating coil treatment

Table 3 In- and exclusion criteria for coil treatment

Inclusion
Severe hyperinflation: total lung capacity >100% of predicted, and RV >200% of predicted and RV/TLC >58%
Post bronchodilator FEV_1 <45% of predicted
6MWD between 150–450 meters
CT confirmed bilateral emphysema
Optimal disease management
Stopped smoking
Vaccinations
Nutritious support
Physically fit/post rehabilitation
Optimal medication
Oxygen suppletion when needed
Bilevel positive airway pressure therapy (BiPaP) when needed
Exclusion
Severe hypercapnia (pCO_2 >7.5 kPa/55 mmHg) or hypoxemia (pO_2 <6.5 kPa/50 mmHg)
Post bronchodilator FEV_1 <15% of predicted
DL_{CO} <20% of predicted
Chronic bronchitis & asthmatic phenotypes
Clinically significant bronchiectasis
Severe recurrent respiratory infections requiring more than two hospitalization stays within the past 12 months
COPD exacerbation within 6 weeks before treatment
Lung carcinoma or pulmonary nodule on CT scan requiring chest CT scan follow-up
Giant bulla of more than one third of the lung field on chest CT
Past history of lobectomy, lung volume reduction surgery, lung transplantation
Pulmonary hypertension (right ventricular systolic pressure >50 mmHg on cardiac echo)
Significant congestive heart failure
Alpha-1 antitrypsin deficiency
Anticoagulants that cannot be permanently stopped
Allergy to nitinol or one of its components: nickel and titanium

RV, residual volume; TLC, total lung capacity; FEV_1, forced expiratory volume in 1 second; DL_{CO}, diffusing capacity of the lung for carbon monoxide; 6MWD, 6-minute walking distance.

have been published until now, reporting the results of 452 treated patients up to 12 months after coil treatment. In these trials, the coil treatment results in significant improvements in pulmonary function and especially quality of life in patients with severe hyperinflation.

Since treatment can be performed regardless of collateral ventilation status it may be an effective treatment for patients who are not eligible for endobronchial valve treatment or other collateral ventilation dependent interventions. In addition, both patients with a homogeneous and heterogeneous phenotype can be treated. The selection of optimally treated, symptomatic COPD patients with severe emphysema and severe hyperinflation while avoiding significant airway disease such as asthma, chronic bronchitis and bronchiectasis, is key to achieve treatment success.

Several new studies are currently underway: the first one being the "REACTION study: Identifying Responders and Exploring Mechanisms of ACTION of the Endobronchial Coil Treatment for Emphysema" (www.clinicaltrials.gov identifier: NCT02179125), a non-randomised open label multi-center intervention study. The objectives are to gain more knowledge on the mechanism of action, identifying predictors of response and describing the effect on patient-based outcomes of endobronchial coil treatment.

A post-marketing study titled "Changes in Lung Physiology and Cardiac Performance in Patients with Emphysema Post Bilateral RePneu Coil Treatment" (NCT02499380) is aimed at understanding the mechanism of action of the RePneu coil by observing changes in lung physiology and cardiac performance in patients treated with RePneu coils.

Another study: "LVRC-Micro: Lung Volume Reduction Coil Microbiome Study" (NCT03010566), aims to investigate possible changes in the microbiome of the lungs in patients 6 months after initial coil treatment.

An overview of current ongoing studies on coil treatment can be found in *Table 4*.

Future research is necessary to provide more insight in different aspects of the coil treatment. Whilst studies investigating the mechanism of action of the intervention and predictors of response are underway, more work is needed to refine patient selection, assess durability of treatment benefit and determine long term cost-effectiveness.

Table 4 Ongoing studies on lung volume reduction coil treatment

Study title	Trial registry number
Endoscopic lung volume reduction coil treatment in patients with chronic hypercapnic respiratory failure	NCT02996149
Improvement of sleep quality by RePneu coils in advanced pulmonary emphysema	NCT02399514
Clinical study to evaluate the exercise capacity in patients with severe emphysema treated with coils (CYCLONE)	NCT02879331
Post market observational, prospective, multi-center study	NCT01806636
COPD Co-pilot air substudy of CLN0014 (Co-Pilot Air)	NCT03267992
Lung volume reduction via coils in patients with COPD	NCT02246569
LVRC IDE crossover study (crossover from IDE Trial CLN0009) (RENEW-CROSSOVER)	NCT02059057
Hyperinflation assessment after treatment by lung volume reduction coil (HEAT-LVRC)	NCT02835001

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Footnote

Conflicts of Interest: JBW declares no conflict of interest. DJS is a physician advisor to PneumRx/BTG, is a principal investigator for trials sponsored by PneumRx/BTG, and received lecture and travel fees for case support, educational and scientific sessions.

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