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 α₁-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...
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 relieve 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 system.
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 (FEV1), 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

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

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 FEV₁ 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 FEV₁, 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up (months)</th>
<th>6</th>
<th>12</th>
<th>3</th>
<th>12</th>
<th>T158:C157</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slobos 2015 (meta analysis)</td>
<td></td>
<td>125</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shah 2013 (RESET)</td>
<td></td>
<td></td>
<td>96</td>
<td>T23:C23</td>
<td>T44:C47</td>
<td></td>
</tr>
<tr>
<td>Deslée 2016 (REVOLENS)</td>
<td></td>
<td></td>
<td></td>
<td>+10.4%b</td>
<td>10.6 (1.1 to 20.1)</td>
<td>+11 (5.2 to ∞)</td>
</tr>
<tr>
<td>Sciurba 2016 (RENEW)</td>
<td></td>
<td>T44:C47</td>
<td></td>
<td>+14.6 (97.5% CI: 0.4 to ∞)</td>
<td>+10.4%b</td>
<td>+10.6 (1.1 to 20.1)</td>
</tr>
</tbody>
</table>

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 FEV1, 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 FEV1 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 FEV1 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 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...
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 trial 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 supplementation 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.
Welling and Slebos. Lung volume reduction coil treatment

Acknowledgements

None.

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.

References


| 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 RePnue 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 |


