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Review Article

Endobronchial coils – therapeutic innovations for severe emphysema

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ABSTRACT

Emphysema is a frequent phenotypic manifestation of chronic obstructive pulmonary diseases which does not respond to pharmacotherapy. Interventional methods can provide relief for severely ill and highly symptomatic emphysema patients. A quite well studied endoscopic method is the minimally invasive, non-surgical procedure with coils. Coils are small, shape-memory Nitinol implants designed to gather and compress lung tissue, re-tension the diseased airway network and increase the elastic recoil in the emphysematous lung. To date, the positive benefit-risk ratio of coils is documented by several well-designed randomized clinical trials.

Keywords: obstructive pulmonary disease, emphysema, volume reduction, endobronchial coils

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Introduction

Chronic obstructive pulmonary disease (COPD) is an increasing cause of mortality worldwide. Its prevalence, morbidity and mortality vary across countries. Often, the prevalence of COPD is directly related to the prevalence of tobacco smoking, although in many countries, outdoor, occupational exposures and indoor air pollution are major COPD risk factors [1].

Emphysema

COPD is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases [1]. Two clinically relevant phenotypes exist: chronic obstructive bronchitis/bronchiolitis and emphysema. The chronic inflammation causes structural changes, destruction of parenchyma and narrowing of the small airways [1]. Alveolar attachments are destroyed and abnormal enlargement of air spaces distal to the terminal bronchioles occur, which are typical for emphysema. As a result, the gas exchange surface is reduced and lung elastic recoil decreases. Due to the decreased elastic properties of the lung tissue, small airways collapse during expiration which can cause irreversible hyperinflation [1].

Hyperinflation is described by residual volume, emphysema is diagnosed in radiology. Computed tomography (CT) is a sensitive technique for the detection of emphysema [2]. Functional tests alone are insufficient to quantify the extent of parenchymal loss. However, measurement of diffusion capacity can provide information on the functional impact of emphysema and is often helpful for patients with breathlessness that may seem out of proportion with the degree of airflow limitation [1].

Emphysema is a frequent phenotypic manifestation of COPD which does not respond to pharmacotherapy. Apart from that, many patients suffering from emphysema show at least a certain degree of inflammation, which should be treated with adequate medication [1]. Patients with emphysema commonly suffer from dyspnea [3], which can affect all aspects of everyday life.

Surgical and interventional therapy

Interventional methods can provide relief for severely ill and highly symptomatic emphysema patients. To date, several therapy options exist. The first method to reduce lung volume in patients with severe emphysema was lung volume reduction surgery (LVRS) [4]. Referring to the NETT trial, LVRS yields a survival advantage for patients with both predominantly upper-lobe emphysema and low base-line exercise capacity. Apart from that, variable impact on mortality using this technique was reported [5]. The demand has led to the development of therapeutic approaches applying endoscopy, i. e. endoscopic lung volume reduction (ELVR).

Endobronchial coils – new therapeutic options for severe emphysema

A quite well studied endoscopic method is the minimally invasive, non-surgical procedure with coils [6-13]. Coils are small, shape-memory Nitinol implants designed to gather and compress lung tissue, re-tension the diseased airway network and increase the elastic recoil in the emphysematous lung. The re-tensioning effects of the coils may also tether small airways open, helping to prevent airway collapse during exhalation. Coils are applicated bilaterally in two interventions. Currently, two first-in-man studies [6,7], three feasibility trials [8-10]9 and one published randomized controlled (RCT) pivotal [12] study confirm the benefit of the technology for patients with severe emphysema.

First-in-man and feasibility trials with coils

The first first-in-man trial was published by Felix Herth and collegues in 2010 [6]. 11 patients with severe emphysema underwent 21 procedures. Per procedure 4.9 ± 0.6 coils were placed. During the total follow-up time of 7 – 11 months 33 adverse events were reported, none of them severe. No pneumothorax occurred. The authors concluded that endoscopic lung volume reduction with coils was safe and feasible.

A second first-in-man trial by Dirk-Jan Slebos and colleagues was published in 2012 [7]. 16 patients with severe heterogeneous emphysema were included. Four patients were treated in one lung, 12 were treated bilaterally. 6 months after treatment, significant effects were observed: SGRQ total score improved by 14.9 points, FEV1 by 14.9% and 6-minute walking distance (6MWD) by 84.4 m. All results were significant ($P < 0.005$). Observed adverse events within the first 30 days after intervention were 1 pneumothorax, 2 cases of pneumonia, 6 COPD exacerbations, 4 cases of chest pain and 21 cases of mild hemoptysis (< 5mL). Authors concluded that treatment with coils was a promising technique for treatment of patients with severe heterogeneous emphysema resulting in significant improvements in pulmonary function, exercise capacity and quality of life, with an acceptable safety profile.

The RESET trial [7] by Pallav Shah and colleagues was the first randomized controlled trial with coils in

advanced stage of emphysema, published in 2013. 23 patients with severe emphysema were treated with coils and compared to a control group of 23 patients treated with conservative therapy. After 3 months, significant improvements were observed in the treatment group: FEV1 increased by 14.19%, compared to 3.57% in the control group (P = 0.03). The 6MWD was 51.15 m longer in the treatment group, compared to a decline by 12.39 m in the control group (P < 0.001). RV improved significantly as well. Complications were rare cases of exacerbations, pulmonary infection and pneumothoraces. No significant differences between the treatment group and the control group were observed concerning serious adverse events.

Karin Klooster and colleagues published a feasibility trial in patients with homogeneous emphysema in 2014 [10]. The study included 10 patients, who were treated bilaterally. The primary endpoint of the study was the improvement in 6MWT. At 6 months, 6MWD had improved from 289 to 350 m. FVC, RV and SGRQ total score had significantly improved as well. The study showed, that the benefit of coil treatment is not limited to patients with heterogeneous emphysema, and in contrast to other ELVR-methods patients with homogeneous emphysema can benefit as well.

First long-term data were published by Gaetan Deslee and colleagues in 2014 [9]. 60 patients with severe bilateral heterogeneous emphysema were treated in 11 centers and followed for up to one year. The primary endpoint of the feasibility study was the improvement from SGRQ at 6 months. At 6 and 12 months the mean improvements in SGRQ were 12.1 and 11.1 points, mean improvements in 6MWD were 29.7 and 51.4 m. FEV1 improved by mean 0.11 and 0.11 L and RV declined by mean 0.65 and 0.71 L, respectively. All results were significant (P < 0.01). Post hoc analysis showed significant responses for SGRQ, 6MWT and RV in patients with both heterogeneous and homogeneous emphysema.

To date, the longest follow-up term was observed over a period of 3 years, in 22 Dutch patients. The study confirms the long-term effect of the coils. Clinically relevant improvements were shown to remain, with 40% of the patients reaching the 6MWD minimal important difference, and 59% reaching the SGRQ minimal important difference, respectively [11].

Pivotal trials with coils

The REVOLENS trial [12] by Gaetan Deslee was published in January 2016. 100 patients were enrolled in 10 sites throughout France. The randomized controlled study was funded by the French Ministry of Health. Patients suffered from severe emphysema and represented a broad range of patients in clinical practice. The primary endpoint was improvement of at least 54 m in the 6MWT at 6 months, which is nearly twice the minimal clinically important difference for this test [14]. It was reached by 18 patients (36%) in the coil group and by 9 (18%) patients in the usual care group. After 6 months FEV1 had improved by 9% in the treatment group compared to a decline by 3% in the control group with similar results after 12 months; 8% improvement in the treatment group, 3 % decline in the control group. After 6 months SGRQ had improved by a mean of 11.1 points in the treatment group compared to a mean decline by 2.3 points in the usual care group. After 12 months the improvement in SGRQ in the coil group was mean 9.1 points, compared to a mean decline by 1.5 points in the control group. The most frequent serious adverse event was pneumonia. The magnitude and severity of adverse events were consistent with previous coil studies.

The RENEW trial [13] is the first randomized controlled pivotal trial including patients with homogenous emphysema as well and conducted to support FDA approval. 315 patients took part in the study. The primary endpoint is the mean improvement of 6MWT after 12 months. Secondary endpoints are e. g. changes of FEV1 and SGRQ. As announced recently, all primary and secondary endpoints could be reached. The between-group differences of 6MWD, SGRQ and FEV1 after 12 months were 10.2 m, 8.9 points and 8.8%. The observed adverse events corresponded to the expected safety profile. Pneumothoraces, inflammation of the lower respiratory tract, respiratory insufficiency, hemoptysis, exacerbations and dyspnea were observed more frequently in the treatment group. The data is expected to be published soon. For an overview of randomized controlled trials with coils see Table 1.

Table 1. Overview of results in RCTs with coils compared to the control group

Trial	N	Follow-up (months)	6MWT (m)	SGRQ (points)	FEV1 (%)	RV (L)
RESET (8)	46	3	+63.55*	-8.36*	+10.62*	-0.31
REVOLENS (12)	100	12	+21	-10.6*	+11*	-0.36*
RENEW (13)	315	12	+10.2*	-8.9*	+8.8*	n.a.

** result statistically significant*

6 MWT, 6-minute walk test; SGRQ, Saint George's Respiratory Questionnaire; FEV1, forced expiratory volume in 1 s; RV, residual volume

Ongoing trials

A European register study of patients with severe homogenous and heterogeneous emphysema is currently ongoing and has been recruitung since 2013 and will be followed up for 5 years. 1,250 patients and more than 50 participating centers evaluates patient experiences and collects additional data on the safety and effectiveness of a therapy with coils. It is the largest study for interventional therapy methods in emphysema. The primary objective is a change in SGRQ. Secondary objectives are changes in 6MWD, RV, FEV1 and safety.

Coils – data correspond to clinical practice

All primary endpoints in feasibility and pivotal trials were reached in a statistically significant way. The majority of endpoints were clinically relevant for patients. For minimal clinically important differences of the parameters used in the REVOLENS trial [12], see Table 2. Additionally, the existing data show several advantages of the coils. The method is independent of collateral ventilation [7], which is seen in the majority of patients in clinical practice [15]. Additionally it has been proven to be effective in patients with homogeneous as well as heterogeneous emphysema [9,10]. In clinical practice nearly one third of patients show a heterogeneous pattern [16]. This is in contrast to other ELVR-methods.

Table 2. Minimal clinically important differences used in REVOLENS trial [12]

Test	MCID
6 MWT	25 – 30 m
SGRQ	4 points
FEV1	0.1 L
RV	6.1 – 8.6%

6 MWT, 6-minute walk test; SGRQ, Saint George's Respiratory Questionnaire; FEV1, forced expiratory volume in 1 s; RV, residual volume

For a therapy with coils, several prerequisites have to be met. The Nitinol spirals are an option for severely ill and symptomatic emphysema patients meeting the criteria of GOLD III with severe hyperinflation and a stable course of disease (patients who are not a high exacerbator phenotype, and have not recently been hospitalized for a respiratory event within 3 months). Important contra-indications are pulmonary hypertension, clinically relevant bronchiectasis, giant bullae in chest CT or treatment with anticoagulants. Inclusion and exclusion criteria used in the REVOLENS trial are listed in Table 3.

Table 3. Medical inclusion and exclusion criteria in REVOLENS trial [12]

Inclusion Criteria	Exclusion Criteria
Bilateral emphysema on chest CT scan	Post bronchodilator FEV1 < 15% predicted
Post bronchodilator FEV1 < 50% predicted	Post-bronchodilator change in FEV1 > 20%
Total lung capacity > 100% predicted	Severe recurrent respiratory infections requiring more than 2 hospitalization stays within the past twelve months
Residual volume > 220% predicted	COPD exacerbation requiring hospital stay within 3 months
Dyspnea score between 2 and 4 based on the mMRC scale	Pulmonary Hypertension (Pulmonary systolic pressure > 50 mmHg on cardiac echo)
Stopped cigarette smoking for more than 8 weeks	Patient unable to perform a 6-minute walk test in room air (no restriction on distance)
Pulmonary rehabilitation within the previous twelve months	Giant bulla of more than 1/3 of the lung field on chest CT
	Strictly homogeneous emphysema on chest CT (investigator interpreted)
	Clinically significant bronchiectasis
	Past history of lobectomy, lung volume reduction surgery, lung transplantation
	Any extrapulmonary diseases compromising survival or evaluation within the protocol (severe cardiac disease, severe renal insufficiency, cancer…)
	Lung carcinoma or pulmonary nodule on CT scan requiring chest CT scan follow-up
	Contraindication to general anesthesia
	Oral anticoagulant treatment with vitamin K antagonists
	Allergy to Nitinol

CT, computed tomography; FEV1, forced expiratory volume in 1 s; mMRC scale, modified Medical Research Council dyspnea scale

As a conclusion, in the last years, several new therapeutic options were developed in the area of endoscopic lung volume reduction. The main differences are related to the therapeutic effect, area of application, number and severity of adverse events and quality of scientific data. To date, in contrast to other methods, the positive benefit-risk ratio of coils is documented by several well-designed randomized clinical trials [8,12,13]. Moreover, in the recently updated strategy paper of the GOLD (Global Initiative for Obstructive Lung Disease) expert group on management of COPD patients, endobronchial implantation of valves as well as coils are mentioned as bronchoscopic interventions for selected patients with advanced emphysema. Both techniques can reduce end-expiratory lung volumes and improve the patient's exercise capacity, lung function and quality of life (evidence level B) [1]. Frank Sciurba concluded in his editorial in JAMA with regard to the published pivotal study REVOLENS: "Should the emerging data from larger pivotal trials support the meaningful clinical, albeit palliative, responses observed in preliminary trials, physicians caring for patients with COPD should not delay in providing evidence-based interventions that offer realistic hope to patients with few other choices to relieve their symptoms and improve their quality of life" [17].

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