BRONCHOSCOPIC NITINOL COIL IMPLANTATION: A NEW LUNG VOLUME REDUCTION STRATEGY IN COPD

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ABSTRACT

Emphysema is a progressive, debilitating disease characterised by irreversible destruction of lung tissue. The gas trapping within the destroyed alveoli, and resultant hyperinflation, render conventional medical treatment generally of limited benefit, especially in the advanced stages of the disease. Utilisation of bronchoscopic techniques for achieving lung volume reduction has advanced over the past years. Amongst these, lung volume reduction using coils (LVRC) is a promising option. The LVRC are made from preformed Nitinol wire with shape memory. They are bronchoscopically delivered into the desired sub-segmental bronchus and recover to a pre-determined shape upon deployment. Published data so far, with endpoints being safety and feasibility, are promising. The procedure itself seems to be technically feasible and results in significant improvements in pulmonary function, exercise capacity, and quality of life sustained during the follow-up period, and with an overall acceptable safety profile. Current ongoing studies further investigate the feasibility, safety, and efficiency of LVRC. Future research is necessary in order to elucidate whether the patient selection criteria and methodology currently used are amenable to improvements, and to establish the duration of benefit and its cost-effectiveness when compared to optimal medical treatment, before applying this treatment into routine clinical practice.

Keywords: Chronic obstructive pulmonary disease, emphysema, bronchoscopy, lung volume reduction coils.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) continues to be a significant cause of morbidity, mortality, and healthcare costs worldwide. As the global population ages, the burden of COPD will increase in years to come. Due to the number of current and new smokers, emphysema affecting COPD patients is also expected to remain a leading cause of morbidity and mortality.[1] The overall prevalence of stage II or higher COPD is 10.1%, 11.8% for men, and 8.5% for women, with a pooled prevalence of emphysema ranging close to 2%.[2,3]

Emphysema is a progressive, debilitating disease that is characterised by irreversible destruction of lung tissue as a result of inflammation. This inflammation is caused in most patients by exposure to noxious inhaled agents for extended periods of time, the most common being cigarette smoke.[4] The destroyed alveolar tissue results with disease progression in a decrease in lung elastic recoil, hyperinflation, and gas trapping due to premature closure of the small airways of the affected lung tissue. The gas trapping and resultant hyperinflation render conventional medical treatment, consisting of bronchodilators and anti-inflammatory medications, generally of limited benefit, especially in advanced stages of the disease.[5]

TREATMENT OPTIONS

For COPD patients with severe emphysema, therapeutic options are still limited. Lung volume reduction surgery (LVRS) has been applied as a palliative treatment in selected patients, but although the concept was excellent, the referral of patients has been severely influenced by significant perioperative death and complications.[6-8]

Over the past decade, there have been significant improvements in the field of interventional pulmonology, and progress has been made in utilising less invasive techniques for achieving the desired lung volume reduction. Different techniques are currently available. Amongst these endoscopic lung volume reduction (ELVR) treatment methods, the one-way valve placement is the most widespread so far.[9-13] These valves allow air to escape from the distal lung without 'fresh' air entering the segment during inspiration. Total occlusion of the target lobe is desired, and the best results of lung volume reduction are achieved when total atelectasis is evident after the procedure. In order for a patient to be suitable for ELVR with valves, radiologic evidence of an intact fissure, as a marker for lack of collateral ventilation, is required. Absence of intact fissures will inhibit volume reduction of the treated lobe, indicating the need for ELVR treatments that work independently of collateral ventilation.[14,15] Treatment with lung volume reduction coils (LVRC) overcomes this limiting factor and might serve as an alternative choice in this specific group of patients. The aim of this review is to quote the ELVR technique by means of LVRC.

LVRC AND THE LVRC PLACEMENT PROCEDURE

The LVRC are made from preformed Nitinol wire with shape memory (Figure 1a). They are bronchoscopically delivered straight into the desired sub-segmental bronchus and recover to a non-straight, pre-determined shape upon deployment. A possible mechanism that explains how coils work, is by mechanically bending the airway and compressing the diseased lung parenchyma. In this manner, the coil seems to cause tension in the surrounding tissue, increasing elastic recoil and possibly redirecting air to healthier portions of the lung. LVRC exist in three different sizes (100, 125, and 150 mm) to accommodate differently sized airways.

Going through the whole procedure in greater detail, the LVRC placement requires a specific delivery system. This delivery system consists of a guide wire, a delivery catheter, a cartridge, and forceps. First, the airway in the selected segment is identified bronchoscopically and the low stiffness guide wire is advanced into the airway under fluoroscopic guidance. The catheter is passed over the guide wire and aligned with its distal tip at approximately 15 mm from the pleura. The length of the airway is

Figure 1a.

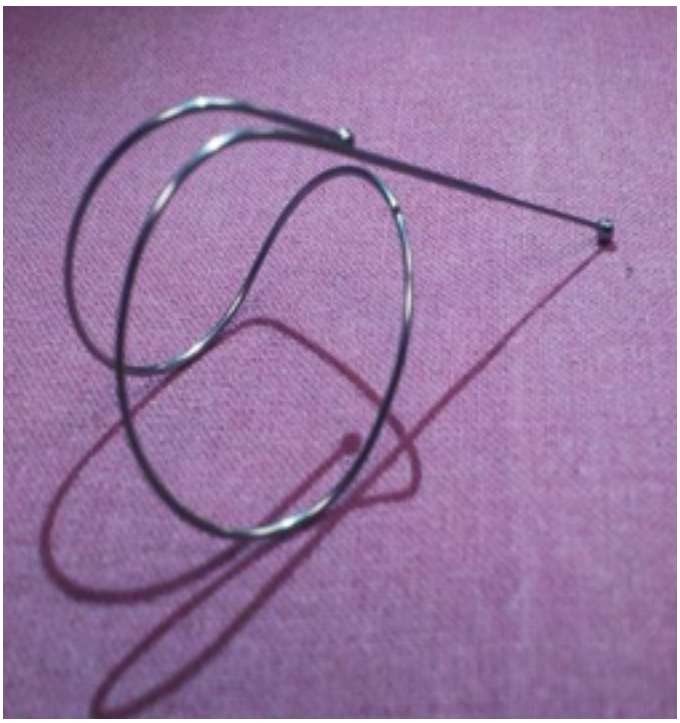

Figure 1b.

Figure 1a. RePneu® Lung Volume Reduction Coil.
Figure 1b. RePneu® Lung Volume Reduction Coil, straightened in cartridge.

measured using radiopaque markers on the guide wire and the desired LVRC length is chosen. The guide wire is then removed and the catheter stays in place. Using the forceps, the endoscopist grasps the LVRC by its proximal end and passes it through the cartridge, which results in the LVRC acquiring a straight form (Figure 1b). The straightened LVRC is then loaded into the distal end of the catheter by coupling the cartridge to the catheter´s hub and the LVRC is then introduced further distally through the catheter with the help of the forceps and under fluoroscopic guidance. Next, the catheter is removed while the proximal end of the LVRC is held in place with the forceps. As the catheter is pulled back, the LVRC assumes its preformed shape, bending the airway and attached parenchyma with it. Finally, the LVRC is released from the forceps and the bronchoscope and forceps are removed (Figure 2). These steps are then repeated in the same sequence for every LVRC to be placed. In the literature, it is mentioned that it is possible to remove or reposition the LVRC by reversing the implantation process,[16] but to our knowledge this can be difficult.

Bronchoscopy can be done under moderate sedation or general anaesthesia according to patient requirements and local practice. Antibiotic prophylaxis according to standard protocols is also common, usually for a total of 7 days. Following recovery from anaesthesia patients must stay in hospital for 1-3 days for observation. Possible post-procedural side-effects, so far observed, include mild to moderate haemoptysis, chest pain, cough, pneumothorax, COPD exacerbation, and pneumonia.

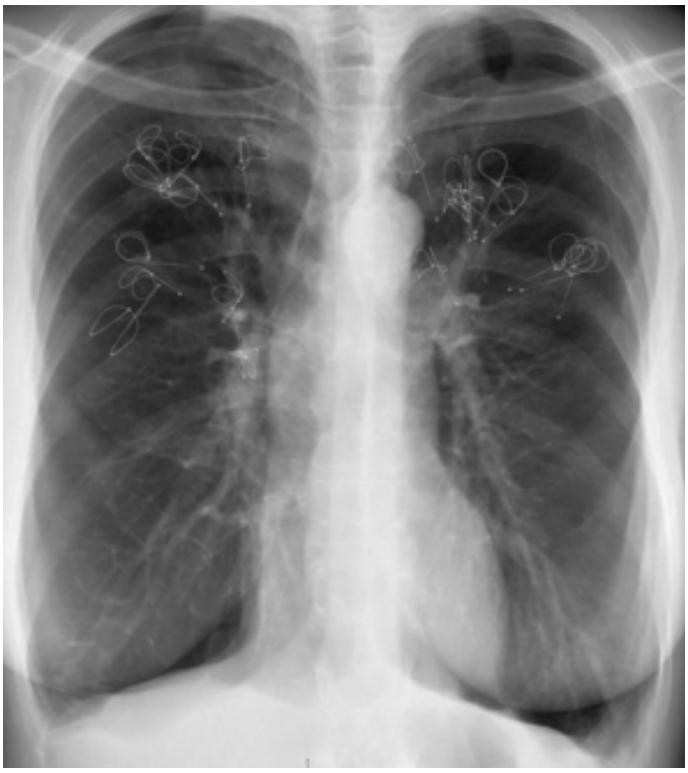

Figure 2. Chest X-ray after bilateral coils insertion. Courtesy of Prof C.P. Heußel.

PUBLISHED DATA

LVRC is a relatively new therapeutic approach and published data so far is meagre. In the first pilot study published, Herth FJ et al.[17] included 11 patients with severe predominantly homogeneous (8 patients) or heterogeneous (3 patients) emphysema and incomplete fissures bilaterally, whose most diseased areas were treated by insertion of coils. These 11 patients underwent a total of 21 procedures. Inclusion and exclusion criteria were modelled on the National Emphysema Treatment Trial (NETT) study and are included in Table 1. The primary endpoints were safety and feasibility, and the secondary endpoints were efficacy outcomes. Safety was measured by the analysis of adverse events. Owing to the sequential treatments and operator discretion, all patients had a total follow-up time of at least 7 and up to 11 months. Each of the 33 adverse events which occurred during the follow-up period, were categorised by severity [mild (36%), moderate (64%), or severe (0%)] and by relationship to device or procedure [not related (42%), possibly related (58%), or probably related (0%)] by the treating physician. Adverse events, rated as possibly related to either the procedure or the device were dyspnoea (10 events), cough (5 events), COPD exacerbation (3 events), and chest pain (1 event). No pneumothorax was noted. Although the study was neither intended nor powered to analyse effectiveness, some interesting trends have emerged, with the predominantly heterogeneous disease group appearing to show substantial improvements in pulmonary function, lung volumes, 6-minute walking test (6MWT), and quality-of-life (QoL) measures.

The study that followed was a prospective cohort pilot study from Slebos DJ et al.,[18] NCT01220908, in which 16 patients were treated (4 unilaterally and 12 bilaterally). This time, the safety and efficacy of LVRC treatment was assessed in patients with severe heterogeneous emphysema, which were followed up for 180 days. Table 1 comprises the inclusion criteria. For safety assessment, all adverse events that occurred were reported. Consequently, they were divided into those occurring during the

Table 1. Main inclusion criteria for three published studies on LVRC treatment of emphysema.

	Herth FJ et al.[17]	Slebos DJ et al.[18]	Shah PL et al.[24]
Age	≥35 years	N/A	≥35 years
Homogenous/heterogeneous emphysema on HRCT	+/+	–/+	+/+
Unilateral/bilateral emphysema on HRCT	+/+	+/+	+/+
FEV1 post-bronchodilation	≤45% pred	<45% pred	≤45% pred
TLC	>100% pred	>100% pred	>100% pred
mMRC score (scale 0-4)	≥2	>1	≥2
Ex-smoker	≥8 weeks	>8 weeks	≥8 weeks
Informed consent	+	NA	+

HRCT: high resolution computed tomography scan, FEV1: forced expiratory volume in the 1 sec, TLC: total lung capacity, mMRC: modified Medical Research Council dyspnoea scale, pred: predicted.

first 30 post-procedural days, rated as possibly related to either the device or the procedure, and those occurring during the follow-up period from 1 to 6 months. In the first instance, the events reported were pneumothorax (1 event), pneumonia (2 events), COPD exacerbation (6 events), chest pain (4 events), and mild haemoptysis (21 events). In the second instance, pneumonia (3 events) and COPD exacerbation (14 events) were reported. All events resolved with standard care. Concerning efficacy, the primary variable assessed was any change in respiratory-related QoL, as estimated by St George's Respiratory Questionnaire (SGRQ); a significant improvement of 14.9 points (±12.1 points, p=.005), and a total score was reported at 6 months compared to baseline. Additionally, pulmonary function testing (PFT) and 6MWT were performed and the initial improvements observed were sustained throughout the 6 month follow-up period with a Δ forced expiratory volume in 1 sec (FEV 1) of +14.9% (±17.0%), Δ functional vital capacity (FVC) of +13.4% (±12.9%), Δ residual volume (RV) of -11.4% (±9.0%), and a Δ 6MWT +84.4 m (±73.4 m), with more than 50% of the patients improving to above the minimal clinical important difference (MCID) for FEV1,[19] 6MWT,[20-22] and SGRQ.[23] (Table 2)

The most recently published trial, up to August 2013, is a prospective, randomised, multicentre trial from Shah PL et al.,[24] which recruited 47 patients with severe emphysema from three centres in the UK. Patients in this study were randomly allocated in a 1:1 ratio to either LVRC treatment (treatment group, 23 patients) or best medical care (usual care group, 24 patients). Inclusion criteria are provided in Table 1. To the patients of the treatment group, LVRC were inserted into the selected lobe or lobes as previously described. Subsequently, patients were reassessed after 1 month, with stable patients (patients with no substantial deterioration of symptoms and on routine medications for at least 14 days) undergoing treatment of the contralateral lung. Treatment group patients were followed by clinic visits at 30 and 90 days after second treatment. The usual care group underwent similar initial clinical assessments and clinic visits to coincide with the two treatment visits. The primary endpoint of the study was the difference in response in the SGRQ between treatment and usual care groups at 90 days after final treatment. Secondary endpoints were changed from the baseline for percentage of change in FEV1, Total Lung Capacity (TLC), RV, 6MWT, and modified Medical Research Council dyspnoea scale (mMRC). The safety outcome of the study was to identify any potential procedure-related and device-related adverse events at 90 days after final treatment. During the initial treatment recovery period (initial 30 days after each treatment or usual care visit), six serious adverse events (2 exacerbations of COPD, 2 pneumothoraces, which responded quickly to intercostal drainage, and 2 lower respiratory tract infections, a total of 15% incidence) were reported in the LVRC group and one in the usual care group (4% total incidence).

Table 2. Results of three published studies on LVRC treatment of emphysema.

	Primary endpoints	Secondary endpoints
Herth FJ et al.[17] *11 patients treated with LVRC* 90 days follow-up	***Safety:*** Total of 33 adverse effects; 36% mild, 64% moderate, 0% severe; 0% probably related to device or procedure, 58% possibly related, 42% not related.	***Efficacy (ΔPFT, ΔmMRC, ΔSGRQ):*** Patients with heterogeneous emphysema trended to achieve better outcomes. The study was neither designed nor powered to evaluate statistical significance.
Slebos DJ et al.[18] *16 patients treated with LVRC* 30 days follow-up	***Safety:*** - pneumothorax, 1 event - COPD exacerbation, 6 events - chest pain, 4 events - mild haemoptysis, 21 events	***Efficacy (ΔPFT, ΔSGRQ, Δ6MWT)*:*** ΔFVC%: + 17.0±14.9, p=.002 ΔFEV1%: + 22.6±21.7, p=.004 ΔRV%: -12.4±9.0, p<.001 ΔRV/TLC%: -8.2±7.1, p=.002 ΔSGRQ: -12.2±13.5, p=.009 Δ6MWT%: +29.8±0.4, p=.006
180 days follow-up	- pneumonia, 3 events - COPD exacerbation, 14 events	ΔFVC%: +13.4±12.9, p=.002 ΔFEV1%: +14.9±17, p=.004 ΔRV%: -11.4±9.0, p<.001 ΔRV/TLC%: -8.0±5.5, p<.001 ΔSGRQ: -14.9±12.1, p<.001 Δ6MWT%: +2.9±36.3, p<.005
Shah PL et al.[24] 90 days follow-up [***2 patient groups:*** ***Treatment group*** (23 patients assigned to LVRC treatment) ***Control group*** (24 patients assigned to control, usual care)]	***Between group difference in SGRQ change from baseline° (intention to treat analysis):*** -8.36 (-16.24 to -0.47), p=0.04	***Between group difference in PFT, 6MWT, mMRC changes from baseline° (intention to treat analysis):*** TLC: -0.11 (-0.29 to 0.07), p=0.22 RV: -0.31 (-0.59 to -0.04), p=0.03 6MWT: 63.55 (32.57 to 94.53) p<0.001 % change in FEV: 10.62 (1.12 to 20.12), p=0.03 mMRC: -0.15 (-0.60 to 0.30) p=0.5

*Data are presented as change from baseline ±SD.

°Corrected for difference between groups at baseline.

LVRC: lung volume reduction coils, PFT: pulmonary function testing, COPD: chronic obstructive pulmonary disease, 6MWT: 6-min walking test, SGRQ: St George's Respiratory Questionnaire, PFT: pulmonary function testing, FEV1: forced expiratory volume in 1 sec, FVC: functional vital capacity, TLC: total lung capacity, RV: Residual Volume, mMRC: modified Medical Research Council dyspnoea scale.

During the next 2 months, and until completion of the follow-up, three serious adverse events were reported in the treatment group and three in the usual care group (exacerbations and lower respiratory tract infections). The results of the analysis included a statistically and clinically significant improvement of SGRQ score (–8.11 [–13.83 to –2.39]) as well as in 6MWT (51.15 m [27.65 m to 74.66 m]) and improvement in the percentage of change in FEV1 (14.19 [6.84 to 21.55]) and reduction of RV (–0.51 L [–0.73 L to –0.30 L]) at 90 days after final procedure. For further results see also Table 2. In all parameters, the changes were greater in the LVRC group than in the usual care group. There was no significant between-group difference observed in the change in mMRC, TLC and also in serious adverse events occurrence.

ONGOING STUDIES

Currently there are several new trials ongoing, or which have recently been completed, that address some of the issues mentioned above. Their data and conclusions should be considered to be preliminary until they have been published in a peer-reviewed journal. Amongst them, a single-arm, open-label study has been recently completed (NCT01421082) which evaluates physiologic parameters directly related to the possible mechanisms of action of LVRC in subjects with homogeneous emphysema. Relative data have been published in abstract form.[25] Several multicentre studies from Germany, France, and the Netherlands have been recently completed (NCT01328899), or are currently recruiting participants (NCT01822795), (NCT01806636), with primary outcomes aiming to validate the safety and clinical efficacy of LVRC as well as its cost-effectiveness. The RENEW study (NCT01608490), a multicentre, randomised, assessor-blinded controlled study of safety and effectiveness of LVRC is expected to follow-up 315 participants from USA and Europe for 1 year. Some of the latest results from research concerning LVRC, presented as abstracts at the European Respiratory Society Congress (2013), further focus on elucidating the mechanism of coils´ action, probably by improving lung compliance[25] and also prove its efficacy in patients with homogeneous emphysema; efficacy sustained for longer periods of time, up to 1 year, both in patients with heterogeneous and homogeneous emphysema has been also addressed.[26,27] In heterogeneous emphysema and bilaterally incomplete fissures, unilateral LVRC showed improvement in exercise capacity, QoL and PFT at 90 days with a tendency to decrease at 6 months post intervention.[28]

DISCUSSION

The above studies show that LVRC, as a novel therapeutic approach of patients with advanced COPD and severe emphysema, seems so far to be promising due to its safety and feasibility. The procedure itself is technically feasible and results in significant improvements in pulmonary function, exercise capacity, and QoL, with an overall acceptable safety profile.

In emphysema patients, as the disease progresses, the lung becomes too large and can neither expand fully nor function effectively within the rigid chest cavity, and this increasing hyperinflation results in reduced exercise capacity. Furthermore, the respiratory muscles are forced to contract at a mechanical disadvantage and consequently, the work of breathing is increased, leading to patients experiencing gradually deteriorating shortness of breath, limited exercise capacity and decreasing quality of life.[29] As Shah et al.[24] pointed out in the RESET trial, the beneficial effects of LVRC could be explained, due to regional compression of the lung and subsequent expansion of better functioning areas of the lungs, and also due to the re-establishment of tethering in the small airways, which improves elastic recoil of the lung. This results in more efficient support of the walls of the small airways, holding them open and preventing premature collapse or narrowing during expiration, resulting in gradual release of trapped gas. This mechanism would also reduce dynamic hyperinflation, explaining the improvement in exercise capacity that has been observed.

Further research is necessary in order to elucidate whether the patient selection criteria and methodology currently used are amenable to improvements. It is also essential to elucidate whether the positive results of LVRC treatment that we have so far, are consistent amongst larger groups of patients, and to also possibly determine which subgroups of patients will have the best outcomes. To date, post-intervention follow-up has been short and long-term results are still not known. We need to establish the duration of benefit and also its cost-effectiveness, when compared to optimal medical treatment before

applying this treatment into routine clinical practice. LVRC treatment remains currently an expensive procedure, performed in highly specialised centres from experienced bronchoscopists.

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