RATIONALE FOR ENDOBRONCHIAL COIL TREATMENT AS THE PRIMARY INTERVENTION FOR PATIENTS WITH SEVERE EMPHYSEMA

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a chronic, progressive, and debilitating disease, particularly in its final stages. The National Emphysema Treatment Trial demonstrated that surgical removal of diseased portions of the emphysematous lung improved clinical and functional status of a subgroup of severe patients with upper-lobe predominant emphysema and low baseline exercise tolerance. However, questions about morbidity, mortality, and costs have all fuelled growing enthusiasm for endoscopic methods of achieving improved clinical outcomes in this poorly-served patient population. Among the various available methods, endobronchial coil therapy is a particularly promising technique that improves exercise capacity, pulmonary function, and quality of life in severe emphysema, with an acceptable safety profile and growing clinical evidence of sustained improvement. Notably, coil treatment appears effective in broader groups of patients than can be treated with other methods or surgery. Coil treatment as the preferred method for treating severe emphysema represents a welcome paradigm shift, given the known limitations of endobronchial valves and surgery. This review addresses the clinical data available to date and proposes an alternate framework for selecting and treating patients with endobronchial coils.

Keywords: Emphysema, chronic obstructive pulmonary disease (COPD), coil therapy, bronchoscopic lung volume reduction.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic, progressive, and debilitating disease, particularly in its final stages. The National Emphysema Treatment Trial (NETT)[1] demonstrated that lung volume reduction surgery (LVRS) can improve clinical and functional outcomes, as well as survival, in a subgroup of patients with heterogeneous emphysema in the upper lobes and low baseline exercise capacity. However, costs related to the surgical procedure, as well as lengthy hospital stays and recovery periods with consequent 'costs' to patients, make surgery an unwelcome option. Many LVR techniques have been developed to achieve the benefits of LVRS endoscopically. In our view, endobronchial coils represent a promising technique, based on patient benefits, broad applicability of the method within the intended population, and workflow integration to routine pulmonary practice. This review will summarise the clinical data available to date and propose a framework for selecting and treating patients with coils.

RATIONALE FOR ENDOSCOPIC TREATMENT OF EMPHYSEMA

Pathophysiology of Emphysema

Emphysema is a progressive subtype of COPD, mainly caused by smoking or environmental pollution. Emphysema is characterised by irreversible airway obstruction leading to lung hyperinflation, dyspnoea, and poor clinical outcomes. It is associated with the destruction of the collagen and fibres within the alveolar walls, consequently causing loss of elastic recoil, air trapping, and reduction of surface area for gas exchange. Hyperinflation then flattens the diaphragm, which impairs its ability to act as the main respiratory muscle, leading to dyspnoea.[2,3] The quality of life (QoL) of patients affected by this debilitating disease is severely impaired and, over time, complications can become life-threatening. Main pharmacologic and therapeutic options include bronchodilators (short/long-acting), glucocorticoids, pulmonary rehabilitation, and oxygen supplementation.[1] Other critical disease management strategies include smoking cessation, pulmonary rehabilitation, and other interventions such as nutrition counselling and mental health support. As disease severity progresses, pharmacologic management and supplemental oxygen fail to alleviate symptoms, leaving a significant population of severe patients with no viable treatment option.

Surgical and Non-Surgical LVR

The rationale for LVR is that removing the most diseased lung tissue would allow re-expansion of compressed, healthier tissue, shifting lung compliance, and restoring the mechanic function of the diaphragm.[4] Both surgical (tissue removal) and bronchoscopic (atelectasis) techniques have been proposed, with clear benefits as well as significant drawbacks. LVRS consists of the surgical removal of 20-35% of the emphysematous tissue of each upper lobe. Its clinical efficacy and safety profile were evaluated in many non-randomised studies,[1,5,12] but the largest clinical study was the multicentre, prospective, randomised, controlled NETT (n=1,218).[1] Primary endpoints were survival and maximal exercise performance at 24 months. LVRS was evaluated against maximal medical therapy, and was most effective in patients with heterogeneous, upper-lobe predominant emphysema, low exercise capacity, and low baseline perfusion to the upper lobes.[13,14] LVRS is, therefore, limited to very severe patients with a specific disease phenotype, yet able to survive high rates of morbidity, which include respiratory failure, prolonged air leak, infection, and thromboembolic events (operative mortality rate, 6%; major pulmonary morbidity, 30%; major cardiovascular morbidity, 20%).[15-19] LVRS is considerably more costly than standard medical therapy; in NETT, its 5-year cost-effectiveness was $140,000 per quality-adjusted life-year gained.[1,20]

Endoscopic LVR (ELVR)

ELVR refers to techniques delivered via a flexible fibre optic bronchoscope, typically requiring a hospital stay of just a few days. Benefits of established techniques include rapid patient recovery and similar or superior clinical improvement versus LVRS, without the morbidity and burden associated with surgery.[21]

Endobronchial/intrabronchial valves

Endobronchial valves (EBV) and intrabronchial valves are one-way valves that are designed to induce atelectasis of the most hyperinflated lobe. When properly placed to fully occlude all airways into a lobe, the one-way valves open upon exhalation, allowing air and fluid to exit the lobe, and close upon inhalation, preventing air from entering the lobe, resulting in eventual lobar collapse, compliance shift toward healthier tissue, and reduction of residual volume (RV). The randomised, controlled VENT trial[22,23] evaluated the use of EBV, in which unilateral treatment was assessed for improvement in forced expiratory volume in one second (FEV_1), dyspnoea, and QoL in 321 patients with severe heterogeneous emphysema. Only modest improvements were observed for all endpoints, resulting in FDA denial of approval.[24]

The challenges of EBV in real-world clinical practice are clear. As summarised in a recent literature review by Shah et al.,[25] and in retrospective analyses of the VENT trial, EBV cannot be used in patients with collateral ventilation (CV) - a condition highly prevalent in severe emphysema, where openings in lobar fissures allow backfilling of air into the treated lobe via the adjacent lobe.[25] The proportion of patients that respond to EBV treatment improves from 20% in the unselected population (i.e. VENT) to 75% with appropriate patient selection. Fissure analysis can be conducted via high-resolution computerised tomography (CT), using

a threshold of >90% integrity to select patients for EBV treatment.[1] In the European cohort of the VENT trial, only 33% of patients had an intact lobar fissure, indicating a need for a treatment strategy uninhibited by this condition. A major limitation of CT fissure analysis, however, is the subjective nature of visual quantification and inconsistency in assessing the degree of integrity.[26] A system to directly assess CV requires that the patient undergo a bronchoscopic procedure during which the pulmonologist will perform a visual, subjective assessment of changes in pressures and flow within the target lobe, fully occluded by a specialised balloon catheter. The system has been demonstrated to have an overall predictive value of only 75%.[27]

Baseline perfusion is another consideration for valve therapy. A retrospective analysis of the VENT trial[28] showed that heterogeneous patients with high baseline perfusion have worse exercise capacity outcomes following EBV-induced atelectasis of a contributing lobe. Therefore, baseline perfusion testing is a critical consideration for valve therapy. Finally, very recently, a National Institute for Health Research (UK) protocol was approved to evaluate EBV treatment in patients with COPD, in which patients will be excluded if they "would be unlikely to survive a pneumothorax if it occurs."[29] This relates to a known and potentially severe consequence of the valve's mechanism of action, namely, atelectasis-induced pneumothorax.

Nitinol coils

The endobronchial coil is a nitinol (nickel-titanium) shape-memory coil that is designed to mechanically increase elastic recoil in the diseased lung by gathering and compressing lung parenchyma. It is straightened for delivery into the target sub-segmental airway, deployed via a specialised catheter, and regains its three-dimensional shape as it is released, with the effect of shortening the airway and thereby increasing regional radial tension. Approximately ten coils distributed evenly throughout the target lobe appear to yield significant and sustained clinical benefit,[30] although clinical and commercial experience suggests that the larger lower lobes may require more coils.[31]

The mechanism of action of coils is unique as it does not rely on atelectasis; rather, the mechanical re-tensioning of tissue appears to improve lung mechanics as well as support radial suspension of airways, preventing airway collapse and dynamic hyperinflation. This unique mechanical function is believed to explain the significant improvements in exercise capacity seen in patients treated with coils, despite a less impressive increase in FEV_1.[32] As the coil is not a blocking device, it does not rely on the absence of CV to produce clinical improvements. Thus, a significant step in the screening process can be eliminated, saving time and expense, as well as preventing patients from undergoing an additional bronchoscopic procedure. As the coils are not shunting devices, it is believed that they do not compromise, or significantly impact perfusion within the treated lobe. Finally, because EBV is reserved for patients in a severe and therefore frail state, the comorbidities associated with any treatment must be considered. Atelectasis-induced pneumothorax rates in patients treated with valves are increasing as patient selection improves, and as pneumothorax does not always occur before hospital discharge, patients and families must be aware of the signs of pneumothorax so that prompt medical attention can be sought.

Coil treatment involves two separate procedures to treat two contralateral lobes. CT-based patient selection involves visual analysis to exclude patients with severe bullous disease, suspicious nodules, active infection, and insufficient residual parenchyma according to a 0-5 point visual scale.[33] The most visually damaged lobe on either side will be treated. The procedure takes 20-30 minutes depending on patient anatomy and physician experience. The objective of this treatment is to place approximately ten coils sub-segmentally, distributing the coils evenly throughout the lobe (Figure 1). Deployment is achieved under fluoroscopic guidance. Three coil sizes are available (100/125/150 mm) and correspond to the total length of the device. Unlike valve procedures - where sizing and placement is absolutely critical in order to avoid missed lobar occlusion, expectoration, and/or migration - success of coil treatment does not appear dependent on specific placement within the patient's anatomy, and coils do not appear to migrate/dislodge, even up to 3 years post-implantation.[34]

Other Bronchoscopic Techniques

Other ELVR techniques include biologic volume reduction with a sealant to collapse diseased tissue,[35-37] thermal airway ablation,[38,39] and airway bypass.[40] These will not be discussed in this paper as they have achieved limited success and are not currently in clinical or commercial use.

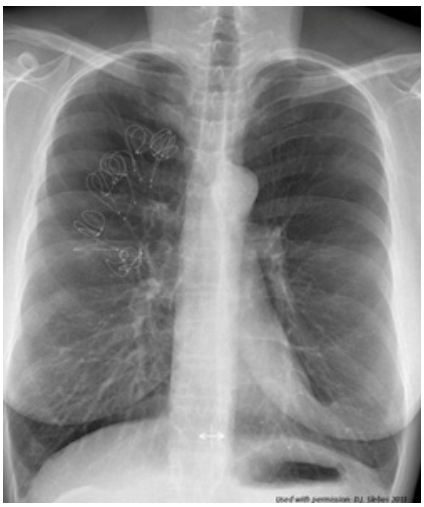

Figure 1: Sub-segmental coil placement, first treatment. Objective is to achieve even distribution of coils throughout the sub-segmental region.

LVR COIL TREATMENT

Rationale as First-Line Therapeutic Option in Severe Emphysema

As discussed above, LVRS and EBV are useful techniques that can alleviate symptoms and improve clinical outcomes. However, their applicability is limited to patients with upper lobe heterogeneous disease and low baseline perfusion, while CV (a factor for EBV) and high exercise capacity further restrict the patient pool.[25] Importantly, neither method has been proven effective in treating homogeneous emphysema, in which the disease is dispersed throughout the upper and lower lobes. As discussed below, coil treatment in homogeneous emphysema has been prospectively evaluated, and growing clinical and commercial experience demonstrates its effectiveness in the majority of severe patients who present with homogeneous disease.

Review of Data Supporting LVR Coil Treatment

To date, four clinical publications describing coil treatment of severe emphysema are available, including one published randomised, controlled trial. Two large-scale randomised, controlled trials are ongoing or awaiting publication.

Pilot studies

Slebos et al.[41] published results of a prospective cohort pilot study in 16 patients with severe heterogeneous emphysema, of whom, 12 received bilateral treatment and 4 unilateral treatment, for a median of 10 coils per patient.[41] At 6 months, QoL as assessed by St George's Respiratory Questionnaire (SGRQ; -14.9±12.1 points), FEV_1 (+14.9%±17.0%), forced vital capacity (FVC; +13.4%±12.9%), RV (-11.4%±9.0%), and exercise capacity as assessed by the 6-minute walk test (6MWT; +84.4 m±73.4 m) were all significantly ($p<0.005$) improved from baseline. Deslee et al.[30] published the results of a multicentre European feasibility study on 60 patients, of whom 55 were treated bilaterally.[30] Per protocol, 34 patients completed 12 months follow-up, demonstrating sustained benefits from treatment at 1 year (6MWT +51.4±76.1 m, $p=0.003$; SGRQ -11.1±13.3, $p<0.001$; FEV_1 +0.11±0.3 L, $p=0.037$; RV -0.71±0.81 L, $p<0.001$). Serious adverse events (SAEs) within 30 days of treatment included COPD exacerbation (n=7), pneumonia (n=6), pneumothorax (n=4), and haemoptysis (n=1). In a single-arm, open-label feasibility study, Klooster et al.[31] reported on 10 patients with strictly homogeneous emphysema and hyperinflation, receiving bilateral treatment with a median of 11 coils in each lobe.[31] Exercise capacity was improved (6MWT, 289 to 350 m, $p=0.005$), as well as the FVC (2.17 to 2.55 L, $p=0.047$), RV (5.04 to 4.44, $p=0.007$), and QoL (SGRQ, 63-48, $p=0.028$). A significant decrease in volume-dependent airway resistance was also observed after bilateral treatment, suggesting improvement in lung compliance, and supporting the mechanism of action of airway tethering. In total, 140 patients were treated in 4 European clinical studies with similar protocols and inclusion/exclusion criteria, as reported in peer reviewed publications, including one randomised, controlled study.

Randomised studies

RESET[42] was the first non-blinded, multicentre, randomised study on 47 patients with severe emphysema and severe hyperinflation.[42] Patients were 1:1 assigned either to treatment or best medical care. The primary endpoint was QoL, as evaluated by improvement in SGRQ 90 days after final treatment (approximately 6 months post-baseline). The SGRQ difference was -8.39 points in favour of the coil group. Coil treatment also improved exercise capacity (6MWT +63.55 m, $p<0.001$) and pulmonary function (RV -0.31 L; FEV_1 +10.62%). In 2012, the French Ministry of Health approved and funded a 1:1 randomised, controlled trial (REVOLENS)[43] to evaluate the clinical benefits

and cost-effectiveness of bilateral coil treatment in patients with severe emphysema.[43] The project recruited 100 patients from 10 French centres and completed enrolment in October 2013, 5 months early. Following 1-year study completion, treatment on control patients is currently ongoing under a crossover protocol; results are expected in early 2015. In 2013, enrolment commenced in an FDA-approved multicentre, 1:1 randomised pivotal clinical trial, RENEW.[33] Up to 30 centres, including 5 in Europe and 1 in Canada, will enrol 315 patients by the end of 2014. The study will evaluate safety and effectiveness of coil treatment versus standard medical care with primary endpoint of 6MWT and secondary outcomes of QoL (SGRQ) and lung function. Patients with heterogeneous and homogeneous emphysema are included; control patients are able to receive treatment via a separate FDA-approved protocol at the 1-year study exit. A European multicentre registry is also actively enrolling patients in a number of European countries, with 6-month results on 100 patients expected in 2014.[44]

Patient Selection Algorithm

Patients with severe (Gold III/IV), stable, and symptomatic emphysema should be considered for a bronchoscopic or surgical intervention. In our view, determination of the most appropriate treatment should follow a comprehensive clinical evaluation, including high-resolution CT scan and recent exercise capacity and pulmonary function tests. Our routine criteria for eligibility include severe emphysema, either heterogeneous or homogeneous, RV ≥200% predicted, and total lung capacity >100% predicted. 'Pink puffers' are excellent candidates; 'blue bloaters' are less likely to respond. Patients with severe bullous disease, known in pulmonary hypertension, prior surgical lung treatment, chronic steroid use, or carbon monoxide diffusing capacity <20% predicted are not candidates for any endoscopic or surgical treatment. It is our opinion that coil treatment should be the primary intervention for patients who meet the above criteria. The selection process for coils is far less complex, less costly, and less time-consuming than that for valves. Far more patients will qualify for coil treatment, and our experience with coils suggests that a 75-80% responder rate can be expected. When patients lack sufficient parenchymal structure for coil treatment, then they may undergo additional testing to determine if valve treatment is appropriate. In our view, this approach is more workflow-efficient, cost-effective, and prevents patients from undergoing unnecessary testing for a procedure that a majority cannot benefit from.

Commercial Experience

In 2010, the coil received Conformité Européenne mark and was made available to selected, trained centres in Germany. As clinical and commercial experience with the technology has expanded, centres in Switzerland, the Netherlands, UK, Spain, Italy, France, and Turkey have started local or regional emphysema coil treatment programmes and/or studies, with results routinely presented at key respiratory congresses. At the American Thoracic Society 2014, three centres in northern Germany reported on 49 patients treated with coils using a similar selection and treatment algorithm.[45] 62 coil procedures were completed in 49 patients. Mean 1-month follow-up data were available for 41 patients (82%). Coil treatment led to a considerable improvement of 6MWD after bilateral procedures (+119±135 m; p=0.006; n=20), after the first procedure (44±131 m; p<0.001; n=41) and the second procedure (+64±110 m; p=0.097; n=20). In the bilateral group, benefits were highly significant and sustained for at least 1-year post-treatment across three centres. Coil therapy was further explored in a retrospective analysis on 26 patients with heterogeneous emphysema and incomplete fissures at Heidelberg University.[46] Notably, these patients were only treated in one lung. Pulmonary function, as assessed by FEV_1 and 6MWT was improved at 3 months but tended to decrease at 6 months follow-up. QoL (SGRQ) was significantly improved at 3 months. These results would appear to support the superiority of bilateral coil treatment for a bilateral disease.

Patient Management Following Coil Treatment

The most frequently observed severe adverse events associated with the use of coils include COPD exacerbation, pneumonia, transient chest pain, and rarely, mild haemoptysis, with low rates of pneumothorax (5-8%) being reported in the literature.[30,46] Most adverse events, in published studies with coils, occurred within 30 days following end of treatment and were resolved with standard care; no life-threatening events such as respiratory failure occurred.[30,31,41,45-47] The bronchoscopy itself has a risk profile, established in the EASE Trial,[40] where SAEs associated with a sham bronchoscopy included COPD exacerbation (18%) and pneumothorax (0.8%) within 6 months.[40] It is

therefore important to carefully consider the risk of bronchoscopy against the intended benefit. For this reason, we do not perform repeat bronchoscopies unless absolutely indicated. Management of adverse events following coil treatment is generally feasible with standard care. We tend to follow a standard pre-treatment prophylaxis which includes oral steroids and antibiotics.

CONCLUSIONS

Coil treatment is an effective option in a majority of patients with severe emphysema for whom medical management is no longer effective. The method improves exercise capacity, QoL, and pulmonary function, while presenting a very good safety profile. It is effective in both heterogeneous and homogeneous emphysema, and does not require complex diagnostic procedures to pre-qualify patients for treatment. We recognise that coil treatment as a primary intervention for the management of severe emphysema may represent a paradigm shift. We invite our colleagues to consider that the coil's mechanical airway tethering mechanism of action is superior to the atelectasis mechanism of valves, and that the simplified patient selection algorithm for coils is far more workflow and cost-efficient, with a similar benefit to patients. We expect the randomised controlled trials in larger patient populations to validate the 'coils-first' approach as access to these endoscopic treatment methods continues to expand.

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