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Emphysema: coiling up the lungs, trick or treat?

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Lung volume reduction coil (LVRC) treatment is a minimally-invasive technique planned to achieve an improvement of exercise capacity and pulmonary function in subjects with advanced emphysema and hyperinflation. It has been proposed together with other bronchoscopic lung volume reduction approaches to reduce lung hyperinflation in emphysema as less invasive alternatives to LVRS and are currently under clinical investigation. Following the successful early experiences in previous pilot trials, recent studies allow further investigation into the feasibility, safety and efficacy of LVR coil treatment in a multi-center setting in a larger group of patients. According to this studies we can state that LVR coil treatment results in significant clinical improvements in patients with severe emphysema, in multicenter analysis, with a good safety profile and sustained results for up to 1 year. The literature on endobronchial coils continues to look promising with an acceptable safety profile, and positive long-term follow-up data are certainly more and more available. However, further well-designed, blinded, placebo (or sham) controlled trials, and even randomized trials against LVRS (lung volume reduction surgery), are needed before routine clinical use can be recommended. This is true not only for endobronchial coils, but also for the whole field of bronchoscopic lung volume reduction.

KEY WORDS: Clinical trials - Emphysema - Pneumonectomy.

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Many subjects suffering from chronic obstructive pulmonary disease (COPD) experience worsening of health related quality of life due to debilitating breathlessness and exercise limitation. Such effects are particularly evident in COPD patients with predominant emphysema.

The emphysematous lungs are characterized by tissue damage with reduction of elasticity. As a consequence, the lungs do not expand and recoil efficiently to drive air through the bronchi to the alveoli and back as the patient inhales and exhales.[1]

Moreover, the decreased lung elastic recoil in emphysema increases expiratory airflow resistance and leads to dynamic hyperinflation.[2]

During exercise, dynamic hyperinflation grows rapidly, decreasing chest wall compliance, impairing respiratory muscle func-

tion, and increasing the work of breathing.[3, 4]

Pharmacological therapy does little to restore these effects of emphysema, even when associated with pulmonary rehabilitation which, improving muscle strengh, can increase exercise capacity without changing though pulmonary pathophysiology.

Treatment options beyond conventional medical therapies are limited to a minority of patients.

Lung volume reduction surgery

Lung volume reduction surgery (LVRS) has been proposed to attain lung volume reduction, mainly by removing the grossly impaired areas of the emphysematous lung.

The rationale of LVRS is to increase lung elastic recoil and decrease end-expiratory lung volume, thereby improving lung and respiratory muscle mechanics and overall exercise tolerance.[5, 6] These approach showed short-term benefit in pulmonary function and dyspnea in highly selected patients [7] with increased survival, one of the most important unmet need in COPD patients, but with safety concerns about mortality and morbidity.

More recently, in selected patients, LVRS has become more widely accepted and bilateral LVRS procedures appear to result in greater short-term improvement than unilateral LVRS.[8]

Bronchoscopic lung volume reduction

Nonetheless a number of bronchoscopic lung volume reduction approaches for emphysema have been proposed as less invasive alternatives to LVRS and are currently under clinical investigation. Such treatments include endobronchial one-way valves, aimed at achieving lobar atelectasis through the unidirectional occlusion of the lobar or segmental bronchi. To date, this has been the most extensively investigated technique in this field.

Endobronchial valves appear to have a very acceptable safety profile. However, successful clinical outcomes from valve therapy can only be achieved in patients with no interlobar collateral ventilation and when the one-way valves are placed to entirely block all the airways into the target lobe. This can be technically difficult due to local anatomy and in the absence of significant experience with these devices.[9] It is estimated that only about 33% of patients with severe emphysema have no collateral ventilation between the target and adjacent lobe and can thus potentially be treated using one-way valves.[10] This clearly shows the need for alternative bronchoscopic treatments that work independently of the presence of collateral ventilation.

Among these lung volume reduction coils (LVRCs) are for sure the most studied non-blocking device.

Coils

Following the successful early experiences in previous pilot trials, a recent study allows further investigation into the feasibility, safety and efficacy of LVRC treatment in a multi- centre setting in a larger group of patients. This is the largest LVRC study to date of its publication, and also evaluated longer-term results of LVRC treatment in a multicentre setting.[11] The key question here is: "Is LVRC treatment feasible and does it sustainably improve quality of life and clinical outcomes in a broad group of patients with severe emphysema treated in a multicentre setting?"

Endobronchial coils certainly appear to have a very good short-term safety profile.

As in previous trials, safety was evaluated by recording all adverse events, efficacy by the St George's Respiratory Questionnaire (SGRQ) as primary endpoint, and pulmonary function testing, modified Medical Research Council dyspnoea score (mMRC) and 6-min walk distance (6MWD). The novelty here is that these data were collected up to12 months after the final treatment.

According to this study we can state that LVRC treatment results in significant clinical improvements in patients with severe emphysema, in a multicenter analysis, with a good safety profile and sustained results for up to 1 year.

Moreover, *post-hoc* analysis of CT scan heterogeneity showed significant responses in both heterogeneous and homogeneous emphysema, suggesting that, in contrast with results from other similar devices, *LVRC*treatment may benefit patients with both heterogeneous and homogeneous disease distribution.

State of the art

LVRC treatment is a minimally-invasive technique planned to achieve an improvement of exercise capacity and pulmonary function in subjects with advanced emphysema.

The Coils work by a mechanical action, specifically the compression of diseased lung parenchyma, due to the physical elastic properties of the Nitinol wire of which the coils are made.

The desired effects of coil treatment are elicited by a reduction of lung volume, similarly to what observed with lung volume reduction surgery.[5] Such benefits are related to the improvement of mechanical properties of the remaining tissue, that may expands following the compression produced by the coils.[12, 13] As a consequence, to obtain the such results, the coils require some minimal amount of lung tissue to compress. Differently from one-way valves, collateral ventilation do not interfere with coils treatment outcomes. Nitinol combines strength and memory shape properties with great elasticity, thereby improving tissue strength and elastic recoil, potentially further reducing the dynamic hyperinflation that occurs easily in these patients.[12]

Few studies have explored the role of endobronchial coils in bronchoscopic lung volume reduction of patients with severe COPD.Preliminary experiences mostly focused on the safety profile of this treatment. In the first pilot study, Herth *et al.* enrolled and treated 11 patients with severe emphysema (GOLD stage 3 or 4) who were followed-up for three months after the last intervention. Ten subjects received a second treatment, in the contralateral lung (6 patients) and in the same lung as the first treatment (4 subjects). The mean number of coils implanted per procedure was five. The primary endpoint was safety, and only in secondary analysis functional data were analyzed.

The procedures resulted well tolerated in all cases. A total of 33 adverse events were registered and none of them were judged as severe. The Authors reported an increase in dyspnoea (6 cases), cough (5 patients), exacerbations of COPD (3 events) and thoracic pain in one subject.

Efficacy data showed meaningful improvements only in patients with heterogeneous emphysema without any significant benefit for subjects with homogeneous emphysema.[14, 15] Slebos *et al.* firstly focused on the efficacy of the lung volume reduction treatment with coils.[16] Twelve patients with severe heterogeneous emphysema were treated bilaterally in two sequential procedures, while in four subjects coils were implanted in one lung only.

In 28 procedures, 260 endobronchial coils (median ten per lung) were placed and none had to be replaced or removed. All the procedures were performed under general anesthesia with an endotracheal tube and flexible bronchoscope under fluoroscopy guidance.

Follow-up data were available at one, three and six months after the final treatment.

Compared with baseline, after six months, the Authors registered a significant improvement in FEV1 (+14.9%), FVC (+13.4%), 6MWT (+84.4 m) with a significant reduction in RV (-11.4%). Quality of life, evaluated with SGRQ, significantly improved (-14.9 points) as well. Bilateral treatment further improved the initial single lung 1-month results.

Furthermore, more than 50% of the patients responded to above the accepted minimal clinical important difference (MCID) for FEV1, 6MWT and SGRQ.

No life-threatening adverse events occurred. The observed complications were represented by one pneumothorax, mild hemoptysis in 12 patients (all resolved spontaneously during the first day) and chest pain

in four cases. At one to six months follow-up, 16 patients experienced a total of 14 COPD exacerbations.

Only one randomized controlled trial compared the efficacy and safety of bronchoscopic lung volume reduction with coils with the best medical care.[17]

At three centers in United Kingdom, 47 patients with severe emphysema were randomized 1:1 to either coils treatment or usual care. The primary endpoint was the difference between change in SGRQ from baseline to 90 days after the final procedure, from treatment and usual medical care. Secondary endpoints were changes from baseline of some functional parameters.

In the coils group, 21 of 23 patients completed the planned bilateral treatment.

Notably, 38 (86%) of 44 procedures were done under local anesthesia and conscious sedation (intravenous midazolam and fentanyl) and only six procedures (in three patients) under general anesthesia.

In 23 treatment patients, 410 coils were implanted with a mean procedure time of 44.9 minutes and a mean number of coils per bilaterally treated patient of 18.5.

Efficacy data showed remarkable superiority of bronchoscopic lung volume reduction arm over the medical treatment group.

The Authors registered a greater improvement of SGRQ, 6MWT and FEV1 from baseline in the coils treatment group than in the usual care arm. The reduction of residual volume was significantly greater in patients treated with coils than in the medical care arm.

On the contrary, no between groups difference in change were detected in mMRC dyspnea score and total lung capacity.

Safety data showed no between-arm differences in serious adverse events.

During the initial treatment recovery period (within the initial 30 days), six serious adverse events were reported in the coils group and one in the usual care group. These events comprised exacerbations of COPD, pneumothoraces and lower respiratory tract infections.

During days 30 to 90 of follow-up, three serious adverse events were recorded in both study arms (exacerbations of COPD and lower respiratory tract infections).

In this study, patients with upper lobe-predominant, lower lobe-predominant and homogeneous disease were all included and, in the opinion of the authors, all had beneficial effects from treatment. Actually, it is worth noting that no specific subgroup analysis was conducted.

Follow-up efficacy data

The presence of collateral ventilation due to incomplete fissures is the major limiting factor in lung volume reduction with endobronchial valves. Treatment with coils overcomes this factor and may serve as an alternative choice in this specific group of patients. Kontogianni *et al*. successfully treated 26 patients with predominantly unilateral heterogeneous emphysema and bilaterally incomplete fissures. Treating unilaterally upper or lower lobes, they demonstrated an improvement in several functional parameters (FEV1, VC, RV, 6MWD, SGRQ) at six months of follow-up in these patients as well.[18]

One study specifically focused on the efficacy of LVR coil treatment in patient with exclusively homogeneous emphysema. Klooster *et al*. enrolled 10 patients with homogeneous disease, placing a maximum of 12 coils in each upper lobe in two sequential procedures. After six months of follow-up, 6MWD, FVC, RV, Raw (airways resistance) and SGRQ resulted significantly improved from baseline. Only two COPD exacerbations and one pneumothorax were recorded as serious adverse events, confirming the safety profile of the treatment also in these patients.[19]

In this literature context, the study by Deslee *et al*.[20] comes out as the largest *LVRC*study to date, firstly reporting data of efficacy and safety after six months and one year of follow-up.

The Authors enrolled 60 patients in 11 European centers. 58 subjects were evaluated at six months (German cohort) and 34 at twelve months. A total of 1125 coils were placed with a median of 10 coils per

lobe. Patients with both homogeneous and heterogeneous emphysema and with lower lobe and upper lobe disease were treated.

At six months of follow-up, efficacy data showed a significant improvement of all the evaluated functional parameters (FEV1, FVC, RV, RV/TLC, 6MWT, SGRQ and mMRC) from baseline, with a magnitude of response in line with the two previous studies on LVR coil treatment.[16, 17]

Moreover, in the 34 patients who completed the 12 months follow-up, there was a sustained improvement of all the key clinical parameters, with mean 6MWT further increased between six and twelve months.

Safety data confirmed a rate of complications comparable to previous reports.[16, 17]

Serious adverse events (COPD exacerbations, pneumonias and pneumothoraces) mainly occurred in the 30 days after the procedure, with all events resolving with regular medical care and without sequelae. The most frequent events were mild haemoptysis requiring no intervention in about one half of subjects and temporary chest disconfort requiring a standard analgesic regimen or no interventions at all.

It should be pointed out that this is the first trial comparing the results for patients with upper versus lower lobe treatment and homogeneous versus heterogeneous emphysema.

Deslee *et al*. failed to detect any outcome difference for RV, 6MWD and SGRQ, when comparing upper with lower lobes treatment. Furthermore, at twelve months after bilateral LVR, no difference between heterogeneous and homogeneous emphysema for FEV1, RV, 6MWD and SGRQ was noted. In the opinion of the Authors, this represents a very important finding, challenging the assumption that only subjects with heterogeneous disease respond to this treatment, as has been shown for surgical lung volume reduction and endobronchial Zephyr valves. They hypothesized that this might be a consequence of the main mechanism of action of coils that are able to re-tension the airways network rather than just reducing lung volume alone.

In the most recent coils study, Hartman *et al*. reported data of effectiveness and safety at two and three years of follow-up of 38 patients who partecipated in two previous pilot study and were invited, after the study completion, for a voluntary annual follow-up.[21]

Safety data fully confirmed the results by Deslee *et al*., with only two post-treatment pneumothoraces and mild hemoptysis being the early most frequent complication (74% of the patients). Despite of some lower respiratory tract infections throughout the whole follow-up period, no late pneumothoraces, coil migrations, major infectious complications or treatment-related deaths were registered.[11] At 2-year follow-up, 27 patients showed RV, mMRC and the SGRQ score significantly improved when compared with baseline, while at 3-year follow-up, 22 subjects revealed only mMRC being significantly improved compared with baseline values. It is worth noting that the rate of decline of FEV1 did not change after the coil treatment. Nevertheless, the treatment increased FEV1 to the extent that return to pre-treatment baseline levels only after approximately 3 years.

Limits of the recent studies

The results of the prospective multicentre study of LVRC treatment in patients with severe emphysema[11] show an acceptable safety profile associated with a significant and sustained improvement over 12 months in relevant clinical and functional parameters including FEV1, RV, 6MWD and SGRQ.

Significant mean improvements in pulmonary function, exercise performance and symptoms at 1 year were also seen in a subsequent study by Hartman *et al*. [21] with a longer extension of follow up to 3 years, but in that more recent trial there did appear to be a waning of benefit over time, with only the modified Medical Research Council dyspnoea score significantly different at 3 years.

This had already happened before in a similar setting investigating the results of BLVR through airway bypass.[22]

Longer follow up and data verification

TABLE I.—*Summary of studies assessing efficacy and safety of lung volume reduction coil treatment of patients with severe emphysema.*

Author (year)	Study protocol	Patients enrolled (N.)	Primary outcome	N. of coils implanted (median)	Type of emphysema	Functional parameters significantly improved from baseline after follow-up completion (median values)	Follow-up duration (months)	Severe complications
Herth (2010) [14]	PCS	11	Safety	5/lobe	Heterogeneous and homogeneous	NR	3	None
Slebos (2012) [16]	PCS	12	Efficacy (SGRQ) Safety	10/lobe	Heterogeneous	FEV1 (+14.9%) FVC (+13.4%) 6MWT (+84.4 m) RV (-11.4%) SGRQ (-14.9 points)	6	20 AECB 1 PNX
Shah (2013) [17]	RCT	47	Efficacy (SGRQ)	18.5/patients	Heterogeneous and homogeneous	SGRQ, 6MWT, FEV1 and RV in LVRCs arm Vs medical care arm	3	5 AECB 2 PNX 2 LRTI
Kontogianni (2014) [18]	RCS	26	Efficacy (FEV1)	10/lobe	Unilateral heterogeneous with bilateral incomplete fissures	FEV1 (+0.06 l) FEV1 (+3%) VC (+0.32 l9 VC (+12%) RV (-0.42) RV (-14%) RV/TLC (-3%) 6MWD (+46 m) SGRQ (-6 points)	6	7 AECB 2 PNX
Klooster (2014) [19]	PCS	10	Efficacy (6MWD)	11/lobe	Homogeneous	FVC (+0.38 l) RV (- 0.60 l) RV (-22%) TLC (-0.12 l) RV/TLC (-6) 6MWD (+61 m) SGRQ (-15 points) Raw (-0.01 Kpa/l/s)	6	2 AECB 1 PNX
Deslee (2014) [20]	PCS	60	Efficacy (SGRQ) safety	10/lobe	Heterogeneous and homogeneous	FEV1 (+15.3%) FEV1 (+0.11 l) FVC (+0.20 l) RV (-0.65) RV (-11.3%) RV/TLC (-4.5) 6MWD (+29.7 m) SGRQ (-12.1 points) mMRC(-0.6)	6 (German cohort) 12 (French and Dutch cohort)	23 AECB 7 PNX 1 Haemoptysis
Hartman (2015) [21]	RCS	38	Efficacy safety	10/lobe	Heterogeneous and homogeneous	mMRC (-0.05)	36	2 PNX 1 haemoptysis

PCS: prospective cohort studies; RCS: retrospective cohort studies; RCT: randomized controlled trial; SGRQ: Saint George's Respiratory Questionnaire; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; RV: residual volume; LVRC: lung volume reduction coils; TLC: total lung capacity; 6MWD: 6 minute walking distance; mMRC: modified Medical Research Council Dyspnea Scale; AECB: acute exacerbation of chronic brinchitis; PNX: pneumothorax; LRTI: lower respiratory tract infection; Raw: airway resistance; l: liters; s: seconds; Kpa: kilopascal.

over time is needed to confirm these optimistic preliminary results. Efforts to do so are underway and data putting together longer follow up outcomes of patients enrolled in different cohorts from previous trials will be available soon.[23] Also, drawing conclusions from small cohorts of patients can be difficult, and the data are inevitably subject to bias.

Survival bias are almost impossible to avoid in such follow-up studies, with some of the more severely affected patients dy-

ing or being lost to follow-up, and those not benefiting from the initial treatment less motivated to attend for subsequent testing.

In these conditions pulmonary function parameters and quality of life estimations over time can appear to be better than they actually are, this making one cautious when interpreting the results.

Conclusions, unmet needs and perspectives

Altogether, bronchoscopic LVR techniques have shown promise in early clinical trials; ongoing work will establish whether they have a role in the routine management of advanced COPD.

Facilitating LVR bronchoscopically may negate some of the risk associated with surgery, reduce inpatient stay for the procedure and potentially reduce the associated costs.

Nonetheless, as per today only a selected number of patients could be considered for BLVR.

This is because, firstly, there is no trial that directly compares LVRS and BLVR, scientific data comparable to the NETT study is not currently available for the majority of these interventions.

Secondly, none of the bronchoscopic methods are considered in the European Scientific Societies Guidelines nor approved by the FDA.

What we know is that the success of endobronchial valves is highly dependent on lobar isolation and collateral ventilation which, as described above, occurs in a significant number of patients.

Non collateral ventilation dependent techniques (LVRCs) are promising, but require larger randomized trials to confirm efficacy and their safety.

By applying traction forces to lung parenchyma, LVRCs aim to improve hyperinflation and gas trapping by reducing dynamic airway collapse. The mechanism of action is independent of collateral ventilation and could be applied to emphysema that is homogeneous or heterogeneous. The early published data shows promise and more work is currently underway to further develop patient selection pathways to prospectively predict who may benefit.

Given the preliminary nature of most data available, more trials are still needed. Research should be designed as a comparative effectiveness research model, trials need to involve a larger number of participants, with a much longer duration of follow-up.

Possibly different markers of improvement than the ones traditionally used have to be considered in order to measure clinical but more importantly functional benefit.

The literature on endobronchial coils continues to look promising with an acceptable safety profile, and positive long-term follow-up data is certainly more and more available. However, further well-designed, blinded, placebo (or sham) controlled trials, and even randomized trials against LVRS, are needed before routine clinical use can be recommended. This is true not only for endobronchial coils, but also for the whole field of bronchoscopic lung volume reduction.

The purpose of future research trials in this field is twofold: first, to demonstrate sustainable clinically significant benefits, and second to determine those patient characteristics that predict response to each individual technique.

We need more about long term survival, by innovative trials designed with a comparative effectiveness research model, involving a larger number of participants, with a much longer duration of follow-up, and, what is more important, with different markers of improvement than the ones traditionally used in these trial as in earlier studies.

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