COILS FOR THE TREATMENT OF ADVANCED EMPHYSEMA: A GROWING BODY OF EVIDENCE AND ROUTINE EXPERIENCE

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Disclosure: Prof Jean-Marc Fellrath has received honoraria as a consultant and speaker from PneumRx Ltd and Pulmonx.
Support: The authors would like to thank Dr. Caroline Charles for medical writing assistance with this manuscript.
Received: 05.05.16 **Accepted:** 14.11.16
Citation: EMJ. 2016;1[4]:44-51.

ABSTRACT

Endoscopic lung volume reduction (ELVR) mainly comprises endobronchial valves (EBV) and endobronchial coil (EBC) implants. EBV aims to occlude the most diseased and/or hyperinflated lobe thus inducing complete atelectasis. EBC therapy was developed a few years ago and is applicable independently of collateral flow and in patients presenting with disease dispersed throughout the upper and lower lobes. Bronchoscopic lung volume reduction with EBC is feasible in a wider range of patients (irrespective of collateral flow or disease homo/heterogeneity) than for EBV, and provides clinical benefits in the short-term, associated to an acceptable safety profile. The growing clinical and commercial experience of ELVR with nitinol coils will be reviewed in this article.

Keywords: Coil, emphysema, surgical management, endoscopic lung volume reduction (ELVR).

INTRODUCTION

Emphysema is a progressive subtype of chronic obstructive pulmonary disease (COPD) which can be particularly debilitating in its advanced stages.[1] The aetiology of emphysema is mainly environmental (smoking and pollution) and leads to the destruction of alveolar walls, irreversible airway obstruction, loss of elastic recoil, air trapping, and thus a reduced gas exchange area. This subsequently generates lung hyperinflation, flattening of the diaphragm, dyspnoea, and poor clinical outcomes with potentially life-threatening complications.[2-5] COPD is incurable and the core of its medical management is aimed at reducing symptoms and disease progression, with smoking cessation, short and long-acting bronchodilators, pulmonary rehabilitation, and oxygen supplementation. In severe emphysema, beyond medical therapy, lung volume reduction, which can be achieved by surgical or endoscopic techniques, redirects airflow to less affected regions.

Lung transplantation and lung volume reduction surgery (LVRS) are the two main surgical modalities demonstrated to improve clinical and functional outcomes.[6] LVRS is the surgical removal of diseased portions (20–35%) of the lung parenchymal volume and aims to improve the efficiency of the remaining intercostal muscles, diaphragm, and lung structure. The National Emphysema Treatment Trial (NETT)[6] demonstrated that LVRS is mainly beneficial in patients with heterogeneous, upper-lobe predominant emphysema, low exercise capacity, and low baseline perfusion to the upper lobes.[6-11] Nevertheless, advanced emphysema is frequently diagnosed in cases with older, frail patients, in which lengthy hospitalisations, long recovery periods, and possible surgical morbidity need to be taken into account.[12-15] For this patient subpopulation, available therapeutic options for severe emphysema are still limited; less invasive techniques to address this unmet need have been developed over the past decade.

This review aims to report on the clinical data available to date (including trial and real-life evidence) on the use of coil therapy for advanced emphysema.

Table 1: Overview of the clinical data available to date on coil therapy in emphysema.

Type of study	n	Indication	Procedure	Coil therapy	Final follow-up	FEV_1 (change, %), MCID ≥12%[41]	FEV_1 % responder rates	FVC (change)	RV (change), MCID ≥0.35[47]		6MWT (change), MCID ≥26 m[48]		SGRQ (change, points), MCID ≥4 points[49]		Study
Pilot Studies															
Single-centre prospective cohort pilot study	11	Heterogeneous and homogeneous emphysema			3M	-5.0±2.9		-1.5±6%	+3.3±4.6%		+5.6±8.5%		-6.1±4.4	79%	Herth et al. 2010[22]
Single-centre prospective cohort pilot study	16	Heterogeneous emphysema	12 bilateral, 4 unilateral treatment	Median 10 coils /patient	6M	+14.9±17.0	64%	+13.4±12.9%	-11.4±9.0%	64%	+84.4±73.4 m	86%	-14.9±12.1		Slebos et al. 2012[35]
Prospective Studies															
Multicentre European feasibility study	60	Heterogeneous and homogeneous emphysema	55 bilateral, 5 unilateral treatment (34 patients completed 12 months follow-up)	Median 10 coils /patient	6/12M	6M: +10.0±21.0% 12M: +8.9±22.2%	48%	6M: +0.20±0.53 L 12M: +0.28±0.45 L	12M: -0.71±0.81 L	65%	+51.4±76.1 m	53%	-11.1±13.3	74%	Deslee et al. 2014[32]
Single-centre prospective cohort pilot study	10	Homogeneous emphysema and hyperinflation		Median 11 coils /lobe	6M			+0.39 L	-0.6 L	70%	+61 m	70%	-15	70%	Klooster et al. 2014[33]
Retrospective Study															
Single-centre retrospective analysis	26	Heterogeneous emphysema and incomplete fissures			6M	0.04±0.12 L	43%		-0.42 L		32±60 m	69%	-6		Kontogianni et al. 2014[36]
Randomised Clinical Trials															
RESET Trial															
Multicentre randomised clinical trial	23	Heterogeneous and homogeneous emphysema			3M	13.8±18.1%	57%	9.5±14.1%	-7.1±10.5%	57%	56.0±65.1 m	74%	-4.7±13.4	65%	Shah et al. 2013[37]
	24		(22 controls treated at crossover)		6/12M	6M: 10.0±21.0% 12M: 8.9±22.2%		6M: 9.6±18.4% 12M: 8.4±16.3%	6M: -5.8±13.6% 12M: -5.4±13.7%		6M: 54.6±54.2 m 12M: 34.1±52.4 m		6M: -7.3±12.2 12M: -6.1±14.0		Zoumot et al. 2015[38]
RENEW Trial															
Multicentre randomised clinical trial	315	Heterogeneous and homogeneous emphysema	Usual care plus bilateral coil treatment Usual care alone	158 157	12M		+7.0% (p<0.001)				+14.6 (p=0.02)		-8.9 points (p<0.001)		[31,34,39]

Table 1 continued.

Type of study	n	Indication	Procedure	Coil therapy	Final follow-up	FEV_1 (change, %), MCID ≥12%[41]	FEV_1 % responder rates	FVC (change)	RV (change), MCID ≥0.35[47]	6MWT (change), MCID ≥26 m[48]	SGRQ (change, points), MCID ≥4 points[49]		Study
Randomised Clinical Trials													
REVOLENS Trial													
Multicentre randomised clinical trial	100	Heterogeneous and homogeneous emphysema usual care plus bilateral coil treatment usual care alone	Usual care plus bilateral coil treatment (n=50) versus usual care alone (n=50)		6M		+0.09 L (95% CI: 0.05 L to ∞; p=0.001)			+21 m (95% CI: -4 m to ∞; p=0.06)		18%; 1-sided (95% CI: 4% to ∞; p=0.03)	6,11,36,37,40-42
					12M		+0.08 L (95% CI: 0.03 L to ∞; p=0.002)			21 m (95% CI: -5 m to ∞; p=0.12)		-10.6 points (95% CI: -5.8 points to ∞; 1-sided p<0.001)	

3M: 3 months; 6M: 6 months; 12M: 12 months; 6MWT: 6-minute walk test; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; MCID: minimal clinically important differences; RV: residual volume; SGRQ: St George's Respiratory Questionnaire.

ENDOSCOPIC LUNG VOLUME REDUCTION

Endoscopic lung volume reduction (ELVR) mainly comprises endobronchial valves (EBV) and endobronchial coil (EBC) implants. EBV aims to occlude the most diseased and/or hyperinflated lobe, thus inducing complete atelectasis.[16-18] However, the patient subset most likely to benefit from EBV is narrow and only allows patients with absence of interlobar collateral flow (i.e. collateral ventilation).[19-21] Nitinol coil therapy was developed a few years ago and is applicable in a wider range of patients, independently of collateral flow.[22] Other ELVR techniques involve the use of a sealant to collapse diseased tissue,[23-25] thermal airway ablation,[26,27] and airway bypass, but these therapeutic modalities have only achieved limited success and are not currently in commercial use.[28] Consequently, the growing clinical and commercial experience of bronchoscopic lung volume reduction with nitinol coils will be reviewed in this article.

ENDOBRONCHIAL COIL THERAPY IN ADVANCED EMPHYSEMA

Principle and Device Technology

EBC implants are nitinol (nickel-titanium) shape-memory devices designed to restore lung elastic recoil through the compression of diseased lung parenchyma and the shortening of the airway, thereby increasing regional radial tension. Their mechanism of action is thus unique, as it does not rely on atelectasis. Tissue re-tensioning improves lung mechanics, prevents airway collapse, and hyperinflation. These translate into clinical benefit, with significant improvements in exercise capacity, and, to some extent, improvements in forced expiratory volume in the first second (FEV_1).[29] Coil treatment success is not dependent on specific placement within the patient's anatomy and coils do not migrate/dislodge (three sizes are currently available; total length: 100/125/150 mm).[30]

Bronchoscopic Procedure

Computed tomography (CT)-based patient selection is first conducted to exclude patients with severe bullous disease, suspicious nodules, active infection, bronchiectasis, small airway disease, severe paraseptal emphysema, or insufficient residual parenchyma.[31] The objective of treatment is to distribute approximately 10 coils sub-segmentally, evenly throughout the lobe under

fluoroscopic guidance. About 10 coils per lobe are set in place and deployed via a specific catheter into their three-dimensional form, but larger lower lobes may require more coils.[32,33] The procedure time is 30–40 minutes, depending on patient anatomy and physician experience.[34] Coil treatment is a sequential bilateral treatment; when treating two contralateral lobes, two separate procedures are involved.

AVAILABLE EVIDENCE BASE FOR COIL THERAPY FOR THE TREATMENT OF ADVANCED EMPHYSEMA

Available Clinical Data to Date

Eight clinical publications describing coil treatment of severe emphysema are currently available, including three published, randomised, controlled trials. Main details on study design, and both clinical and safety outcomes are reported in Table 1.

RECENTLY COMPLETED TRIALS

RENEW Trial

The RENEW trial (NCT01608490) was a pivotal US Food and Drug Administration (FDA)-approved, multicentre, 1:1 randomised clinical trial conducted in 26 centres, including 5 in Europe and 1 in Canada, totalling 315 enrolled patients.[31,34] The study aimed to evaluate safety and effectiveness of coil treatment versus standard medical care with a primary endpoint of 12-months, 6-minute walk test (6MWT), and secondary outcomes of quality of life (QoL) (St George's Respiratory Questionnaire [SGRQ]) and lung function (FEV_1). Patients with heterogeneous and homogeneous emphysema were included; control patients could receive treatment via a separate FDA-approved protocol at the 1-year study exit.

In December, BTG plc (BTG International Ltd., London, UK) announced that all primary and secondary endpoints of the study had been met, with results published in May 2016.[34,39] A statistically significant 14.6 m benefit in change in the 12-months 6MWT was observed over the control group (p=0.02). Similarly, other statistically significant and clinically meaningful improvements versus control group patients in QoL (SGRQ, mean improvement of 8.9 points, p<0.001) and lung function were reported (FEV_1, mean improvement: 7.0%, p<0.001). The respective safety profiles of treatment and control groups were as expected in such patient populations (mostly GOLD IV) and included pneumonia, pneumothorax, lower respiratory tract infections, respiratory failure, haemoptysis, COPD exacerbation, and dyspnoea occurring at a higher rate in the active treatment arm.

REVOLENS Trial

In 2012, the French Ministry of Health approved and funded the multicentre, randomised REVOLENS clinical trial (NCT01822795). REVOLENS was conducted in 10 French university hospitals in order to evaluate 6 and 12-month efficacy, safety, and cost-effectiveness of endobronchial nitinol coil therapy.[40] This superiority trial encompassed 100 patients (71% male; mean age: 62 years), 1:1 randomised to either usual care, i.e. rehabilitation and bronchodilators with or without inhaled corticosteroid and oxygen therapy, or usual care plus bilateral coil treatment with the placement of nitinol coils in both pulmonary lobes.

The primary outcome was exercise capacity improvement of ≥54 m in the 6MWT at 6 months (one-sided hypothesis test). Secondary outcomes included changes at 6 and 12 months in the 6MWT, lung function, QoL as assessed by SGRQ (range: 0–100, minimal clinically important difference ≥4), morbidity, mortality, total cost, and cost-effectiveness. Lung function evaluation comprised FEV_1, forced vital capacity (FVC), residual volume (RV), total lung capacity (TLC), and RV/TLC ratio. Safety was evaluated as adverse event (AE), serious adverse event (SAE) occurrences, and SAE composite scores over the 12-month follow-up period. Patients were followed-up for 12 months.

Efficacy outcomes

Most of the patients assigned to the coil therapy group (94%, n=47) completed bilateral treatment and received a mean of 9.8 coils per procedure. After 12 months, 44 and 47 patients from the coil and the usual care groups were available for follow-up, respectively.

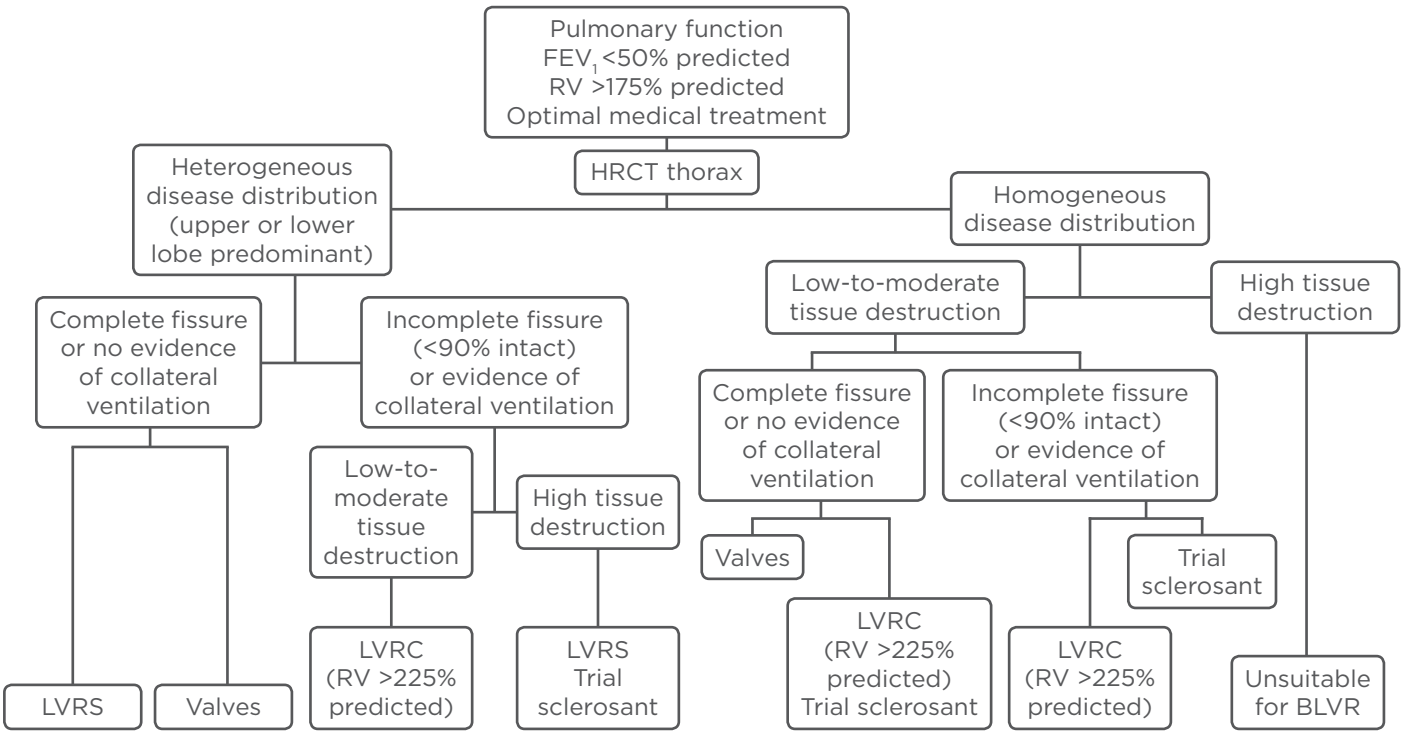
Post-procedure results at 6 months

At 6 months, coil therapy was significantly superior to usual care as the primary endpoint was achieved, with 36% and 18% of patients (evaluable data, n=44 for both groups) reaching an improvement of ≥54 m in the 6MWT from the coil and usual therapy treatment arms, respectively (between-group difference [BGD] of 18%; 1-sided 95% confidence interval [CI]: 4% to ∞; p=0.03).

Table 2: Demographic and bronchoscopic procedure characteristics of the patients at baseline.

Variable	
Age (years)	68±7.7
BMI (kg/m^2)	22±6.1
FEV_1 (L)	0.78±0.29
FEV_1 (% predicted)	31±10
DLCO (% predicted)	38±14.6
RV (% predicted)	227±60
6MWD (m)	310±112
SGRQ	61.8±12.8
Treatment 1: total bronchoscopy time (min)	32.5±10.9
Treatment 1: fluoroscopy time (min)	9±4.2
Treatment 1: number of coils	12±1.38
Treatment 2: total bronchoscopy time (min)	30±11
Treatment 2: fluoroscopy time (min)	8±2.66
Treatment 2: number of coils	11±1.95

Values are reported as median±SD.
6MWD: 6-min walk distance; DLCO: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in the first second; RV: residual volume; SGRQ: St. George's Respiratory Questionnaire; SD: standard deviation.



For any emphysema, a lung transplant should be considered.

Figure 1: Treatment algorithm for bronchoscopic lung volume reduction in patients with severe emphysema.
BLVR: bronchoscopic lung volume reduction; FEV_1: forced expiratory volume in 1 second; HRCT: high-resolution computed tomography; LVRC: lung volume reduction coil; RV: residual volume; LVRS: lung volume reduction surgery.

Significantly different findings were also observed in the secondary endpoints, with 6MWT improvements favouring coil therapy over usual care, the BGD being statistically significant as percentage changes from baseline: 6 months, BGD of +8% (95% CI: -2.7 m to ∞; p=0.048); 12 months, BGD of 7.1% (95% CI: -2.2 m to ∞; p=0.09). At 6 months, coil therapy was significantly superior to usual care in terms of FEV_1 (BGD of +0.09 L [95% CI: 0.05 L to ∞; p=0.001]) and for the other secondary efficacy endpoints (FVC, RV, RV/TLC ratio, Modified Medical Research Council [MMRC] dyspnoea scale, Transition Dyspnea Index [TDI], and SGRQ; all p<0.05). QoL improvement (SGRQ) was superior in the coil treatment group over usual care with a BGD of -13.4 points (95% CI: -8 points to ∞; one-sided; p<0.001).

Post-procedure results at 12 months

At 12 months, BGD were significant (p<0.05) in all endpoints but the 6MWT. As an example, BGD for FEV_1 was +0.08 L [95% CI: 0.03 L to ∞; p=0.002]), again demonstrating statistically significant superiority of coils over usual care. However, the observed BGD did not reach the minimal clinically important difference of 0.1 L.[41] QoL improvement (SGRQ) was sustained at 12 months with superior outcomes in the coil treatment group over usual care (BGD of -10.6 points; 95% CI: -5.8 points to ∞; one-sided; p<0.001). Of note, there was no difference in efficacy between heterogeneous and homogeneous emphysema at both time points.

Safety outcomes

During the 12-month follow-up period, four deaths (8%) were reported in the coil group versus three deaths (6%) in the usual care treatment arm (BGD of 2%; 95% CI: -8–12%; p=0.99). The most frequently reported AE was self-resolving haemoptysis (<5 mL) within 30 days post-procedure (48%). SAE composite scores comprised 17 events in 14 patients (28%) in the coil group and 8 events in 6 patients (12%) in the usual care group (BGD of 16%; 95% CI: 1–31%; p=0.046). Pneumonia was the most frequent SAE and was reported for 11 events in 9 patients (18%) in the coil therapy group and 2 events in 2 patients (4%) in the usual care group during the 12-month follow-up period, with a BGD of 14% (95% CI: 2–26%; p=0.03). Overall, these results show that the safety profile of coil therapy as evidenced in this study was consistent with previous clinical findings,[42] and was similar to that of endobronchial valves[43,44] but much improved over LVRS.[6,11]

Health economics

The mean total 1-year per-patient BGD cost was $47,908 (95% CI: $47,879–48,073, p<0.001). The incremental cost-effectiveness ratio was $782,598 per additional quality-adjusted life-year (95% CI: $663,496–1,327,212 per quality-adjusted life-year). However, as the follow-up period was relatively short (12 months), these findings are insufficient to draw conclusions on the long-term cost effectiveness of nitinol coil therapy since the reported short-term costs should be quantified against the long-term benefits gained post-procedure. As such, this study is still ongoing and encompasses a crossover and an extended (5-year) follow-up, including a long-term health economic analysis of all treated patients.

FROM REAL CLINICAL TRIAL EVIDENCE TO REAL-LIFE CLINICAL PRACTICE: DO THE BENEFITS TRANSLATE INTO THE REAL WORLD?

Real-Life Data on the Commercial Experience of Coil Treatment

PneumRx EBC implant received Conformité Européenne (CE-) Mark in 2010. At the American Thoracic Society (ATS) 2014, data extracted from three centres in Northern Germany reported on 49 patients (62 coil procedures) treated with coils.[45] 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, such benefits were highly significant and were sustained for at least 1 year post-treatment.

In a retrospective analysis on 26 patients with heterogeneous emphysema and incomplete fissures at Heidelberg University, Heidelberg, Germany,[36] 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-month follow-up. QoL (SGRQ) was significantly improved at 3 months. A post-market, observational, prospective, multicentre, European registry is currently recruiting patients.[46]

Experience at Pourtales Hospital, Neuchâtel, Switzerland

Data extracted from the post-market European registry for Neuchâtel Hospital reported on 25 patients with emphysema (48 procedures) treated with coils. Demographic and bronchoscopic procedure characteristics are shown in Table 2. The selection of patients was made according to the algorithm described below. Follow-up data were largely incomplete, being available only for nine patients at 6 months: coil treatment led to a considerable improvement of QoL (SGRQ) after the two procedures (-23.6±9.2, p=0.0009). Pulmonary function (as assessed by FEV_1 and RV) was also significantly improved at 6 months. On the contrary, 6MWD and diffusing capacity of the lung for carbon monoxide did not show any statistically significant change. These very preliminary results are consistent with the already published data.

Treatment Algorithm: Real-Life Clinical Experience

A treatment algorithm for BLVR in patients with severe emphysema is proposed in Figure 1. From our real-life experience and clinical data available to date, BLVR is an option in stable GOLD III/IV patients with homogeneous or heterogeneous emphysema with no massive lung parenchyma destruction and RV ≥175% predicted. Conversely, patients who are not candidates to coil therapy comprise those with severe bullous disease, known pulmonary hypertension, prior surgical lung treatment, chronic steroid use, carbon monoxide diffusing capacity <20% predicted, symptomatic bronchiectasis, and those concurrently receiving any therapeutic anticoagulation or any anti-aggregate therapy other than aspirin.

CONCLUSIONS

Bronchoscopic lung volume reduction with nitinol coils is feasible in a wider range of patients (irrespective of collateral flow) than EBV and provides clinical benefits on the short-term, associated to an acceptable safety profile. However, additional clinical data are still needed to establish the long-term benefit-to-risk ratio of coil therapy; it is likely that further results from follow-ups beyond 12 months from randomised clinical trials will provide answers. These clinical trial data, alongside registry/real-life outcome data, will undoubtedly help refine patient stratification and treatment selection and further ascertain BLVR within the expanding therapeutic armamentarium for advanced emphysema.

Acknowledgements

Medical writing assistance was provided by Dr Caroline Charles of Scilink Medical Writing, Biarritz, France.

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