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Two-year follow-up after endobronchial coil treatment in emphysema: results from the REVOLENS study

To the Editor:

Severe emphysema is a difficult to treat condition with limited efficacy of currently available treatments. Endobronchial coil treatment (ECT) is a minimally invasive endobronchial treatment which consists of placing shape-memory nitinol coils in emphysematous lobes to enhance lung recoil and reduce lung hyperinflation at rest and during exercise [1, 2]. Randomised studies demonstrated an improvement in exercise capacity, lung function and quality of life, and showed an acceptable safety profile at 1 year [3–6]. However, to our best knowledge, longer term safety and effectiveness results beyond 1 year have not been reported thus far.

REVOLENS (Réduction volumique endobronchique par spirales) (NCT01822795) is a 1:1 randomised controlled study of 100 patients (50 patients treated with coils and optimal medical management and 50 patients treated with optimal medical management only) in 10 centres across France. Patients treated with optimal medical management only were offered coil treatment after 1 year. The study protocol [7] and 1-year results [5] of the REVOLENS study have been previously described, demonstrating a decrease in lung hyperinflation and improvement in quality of life. In the present study, we analysed efficacy and safety data at 2 years in the 50 patients randomised to the ECT group. The ethics committee of Dijon Est I and the French Agency for Medicines and Health Products Health approved the study protocol.

Among 50 patients treated by ECT, vital status at 2 years was determined for 49 patients. Four patients died within the first year (one each from peritonitis, mesenteric ischaemia, and chronic obstructive pulmonary disease (COPD) exacerbation; one cause was undetermined) and two patients died within the second year (one from COPD exacerbation and the other from undetermined causes). One patient underwent lung transplantation within the second year. 32 patients attended the 2-year follow-up visit and 11 patients did not. Patients who died or underwent lung transplantation within 2 years (n=7) had lower body mass index (23 ± 4 versus 19 ± 3 kg·m⁻², p=0.03) and forced expiratory volume in 1 s (FEV₁) (27 ± 7 versus $20\pm 4\%$, p=0.02) and higher residual volume (RV)/total lung capacity ratio (0.69 ± 0.06 versus 0.75 ± 0.05 , p=0.03) at baseline, respectively, than those who attended the 2-year follow-up visit (n=32). We also analysed the baseline Saint George's Respiratory Questionnaire (SGRQ) in patients who did not attend the 2-year follow-up (n=11) and found a higher score indicating worse quality of life (70 ± 10 versus 58 ± 12 , p=0.04). Changes from baseline at 6 months, 1 year and 2 years are shown in table 1. The 6-month and 1-year results were comparable for the overall group and for the group of patients attending the 2-year follow-up visit. At 2 years, both RV and SGRQ improvements remained significant, whereas the 6-min walking test (6MWT), modified Medical Research Council dyspnoea scale, and FEV₁ were not statistically different from baseline. While 45 serious adverse events (SAEs) occurred in 26 patients within the first year (0.9 SAEs per patient-year), 27 SAEs in 20 patients occurred within the second year (0.44 SAEs per patient-year). SAEs between the one and 2-year follow-up included 18 respiratory events (12 COPD exacerbation, 4 pneumonia, 1 lung transplant, 1 lung nodule). No pneumothorax, no coil migration, and no unexpected SAEs were observed between one and 2 years of follow-up.

To our best knowledge, this is the first study to report the longer-term safety and efficacy of ECT beyond 1 year from patients randomised to the ECT group in a randomised clinical trial. A strength of this study is the low rate of loss to follow-up with 74% of evaluable patients returning for the 2-year visit. We found



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In severe emphysema, endobronchial coils improve quality of life with an acceptable safety profile at 2 years <http://ow.ly/eVlg30gKrPE>

TABLE 1 Changes from baseline at 6 and 12 months, and 2 years after coil treatment

	Overall group			Patients who attended the 2-year follow-up visit			
	Baseline	6 months	12 months	Baseline	6 months	12 months	2 years
Subjects n	50	47	44	32	32	32	32
6MWT m	300±112	+18±81; p=0.14	-2±87; p=0.88	323±105	+25±67; p=0.048	+15±77; p=0.29	+6±84; p=0.56
≥54 m		16/44 [36%]	8/43 [19%]		12/32 [38%]	7/32 [22%]	7/28 [25%]
≥25 m		19/44 [43%]	12/43 [28%]		15/32 [47%]	11/32 [34%]	11/28 [39%]
mMRC scale	3±0.7	-0.5±0.9; p=0.0002	-0.5±1; p=0.006	2.9±0.6	-0.7±0.9; p=0.0003	-0.7±1; p=0.0007	-0.4±1; p=0.06
≥1		19/47 [40%]	19/41 [46%]		15/32 [47%]	15/30 [50%]	13/30 [43%]
FEV₁ L	0.75±0.25	+0.05±0.14; p=0.02	+0.04±0.15; p=0.1	0.78±0.26	+0.04±0.15; p=0.15	+0.03±0.14; p=0.21	0±0.16; p=0.92
≥100 mL		17/47 [36%]	12/44 [27%]		12/32 [38%]	8/32 [25%]	8/32 [25%]
≥10%		21/47 [45%]	14/44 [32%]		14/32 [44%]	9/32 [28%]	12/32 [38%]
RV L	6.2±0.86	-0.53±0.72; p<0.0001	-0.47±0.68; p<0.0001	5.92±0.74	-0.46±0.51; p<0.0001	-0.39±0.68; p=0.003	-0.28±0.69; p=0.03
≥350 mL		29/47 [62%]	25/44 [57%]		19/32 [59%]	18/32 [56%]	14/32 [44%]
SGRQ (0-100)	60.8±12.8	-11.1±16.1; p<0.0001	-9.1±15.9; p=0.0006	57.9±12.3	-12.3±17.6; p=0.0005	-11.5±16.4; p=0.0006	-7.9±14.5; p=0.005
≥4 points		32/45 [71%]	26/42 [62%]		24/31 [77%]	21/30 [70%]	20/31 [65%]
≥8 points		28/45 [62%]	21/42 [50%]		21/31 [68%]	16/30 [53%]	16/31 [52%]

Data are presented as mean±SD or number (%), unless otherwise stated. The percentage of patients reaching the minimal clinically important difference for each variable is indicated. Changes from baseline were assessed by paired t-tests. 6MWT: 6-min walking test; mMRC : modified Medical Research Council dyspnoea scale; FEV₁: forced expiratory volume 1 s; RV: residual volume; SGRQ: Saint George's Respiratory Questionnaire.

a clinically relevant improvement in coil-treated patients in the REVOLENS study for the SGRQ total score (mean 7.9 points and responder rate 65%) at 2 years. Despite being statistically significant, the magnitude of change in RV (mean 0.28 L and responder rate 44%) might not be clinically relevant. These results are in line with the results obtained in one monocentric study from patients treated by ECT in two early pilot studies and attending voluntary visits at 2 and 3 years [8]. However, our results must be interpreted cautiously owing to limitations in the study. As control patients in our study were offered coil treatment after 1 year, we do not have a control group at 2 years. Outcomes at 2 years after ECT for the control group are not yet available and some patients from the control group were not treated by ECT after 1 year of follow-up because of death, exclusion criteria or patient's refusal. Second, our analyses comparing the 2-year results with baseline data do not take into account the natural clinical and functional decline in severe emphysema, as shown in the control and lung volume surgery groups in the NETT study [9, 10]. We can therefore not exclude that our results at two years underestimate the effects of ECT compared to the natural history of severe emphysema. However, this is likely balanced by a selection bias presumed to occur in long-term follow-up with the best (healthiest) responders more likely to attend follow-up visits. The patients who died or underwent lung transplantation exhibited lower body mass index and FEV₁, factors known to impact survival in COPD. Although our results are exploratory, they suggest that careful risk assessment is important to set appropriate expectations with patients. The patients who did not attend the 2-year follow-up visit exhibited baseline differences including a higher SGRQ score indicating worst quality of life. A potential criticism of the SGRQ results could suppose a placebo effect especially in the absence of a control group. We do agree that for patients with very severe disease refractory to medical management, enrolment in an interventional trial might engender a placebo effect; however, the highly unlikely scenario of a placebo effect maintained at 1 year becomes implausible at 2 years. Our results do show a large variability of response to treatment across a small population, as shown by large standard deviation for each variable at 2 years. Unfortunately, our sample size is too small to conduct multivariate analyses to propose predictive factors of long-term response to ECT. Nevertheless, a strength of this study is pre-specified investigation of all adverse events between one and 2 years after ECT. No unanticipated events occurred up to 2 years, and SAEs decreased after 1 year. No late pneumothorax or haemoptysis events were reported. This is an important finding, as these complications may lead to life-threatening conditions requiring intervention, such as chest tube placement, surgery or bronchial artery embolisation [11]. Long-term tolerability is crucial as the ECT is considered a permanent treatment, although we described a successful late removal of two coils, 10 months after ECT in one patient initially randomised in the usual care group in the REVOLENS study [12]. We acknowledge that adverse events occurring after 1 year in the patients who did not attend the 2-year follow-up visit may not have been reported despite our best efforts, and that underreporting of adverse events reliant on patient recall may also have occurred.

In conclusion, this 2-year prospective follow-up study showed that ECT is associated with a sustained improvement in quality of life, sustained decrease in RV and an acceptable safety profile, with no late-onset or unanticipated events occurring in the one to 2-year post-treatment period. Subsequent 5-year follow-up assessments from REVOLENS and other larger long-term clinical trials will help to better define the long-term effectiveness and safety of endobronchial treatments in severe emphysema and will help to solidify its use in the standard of care.

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