Endoscopic lung volume reduction coils for patients with severe emphysema – a single-center retrospective analysis

Sebastian Mang
Universitatsklinikum des Saarlandes und Medizinische Fakultat der Universitat des Saarlandes
Niklas Hus
Universitatsklinikum des Saarlandes und Medizinische Fakultat der Universitat des Saarlandes
Hans-Joachim Schäfers
Universitatsklinikum des Saarlandes und Medizinische Fakultat der Universitat des Saarlandes
Holger Wehrfritz
Universitatsklinikum des Saarlandes und Medizinische Fakultat der Universitat des Saarlandes
Alexander Massmann
Universitatsklinikum des Saarlandes und Medizinische Fakultat der Universitat des Saarlandes
Christian Lensch
Universitatsklinikum des Saarlandes und Medizinische Fakultat der Universitat des Saarlandes
Frank Langer
Universitatsklinikum des Saarlandes und Medizinische Fakultat der Universitat des Saarlandes
Frederik Seiler
Universitatsklinikum des Saarlandes und Medizinische Fakultat der Universitat des Saarlandes
Robert Bals
Universitatsklinikum des Saarlandes und Medizinische Fakultat der Universitat des Saarlandes
Philipp M. Lepper (philipp.lepper@uks.eu)
Universitatsklinikum des Saarlandes und Medizinische Fakultat der Universitat des Saarlandes
https://orcid.org/0000-0003-3620-0912

Research

Keywords: Endoscopic lung volume reduction, lung volume reduction coils, emphysema, COPD, lung function

Posted Date: August 18th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-60941/v1

Abstract

Background

Patients with chronic obstructive pulmonary disease (COPD) and lung emphysema may benefit from surgical or endoscopic lung volume reduction (ELVR). Previously reported outcomes of nitinol-coil-based endoscopic lung volume reduction techniques have been ambiguous.

Objectives

The analysis was done to analyze outcomes of ELVR with nitinol-coils in patients with severe pulmonary emphysema.

Methods

From September 2013 to November 2014, our center performed a total of 41 coil implantations on 29 patients with severe emphysema. Coils were bronchoscopically placed during general anesthesia. 12 out of 29 patients received contralateral treatments 4-6 weeks later to avoid bilateral pneumothorax. Lung function and 6-minute walking distance were assessed one week prior, one week after as well as 6 to 12 months after the procedure. Patients were followed up to 48 months after ELVR and overall mortality was compared to a historic cohort.

Results

While coil-based ELVR led to significant short-term improvement of vital capacity (VC, + 0.14 l ± 0.39 l, p = 0.032) and hyperinflation (ΔRV / TLC -2.32% ± 6.24%, p = 0.022), no significant changes were observed in 6-minute walking distance (6-MWD) or forced expiratory volume in one second (FEV1). Benefits were short-lived, with only 15.4% and 14.3% of patients showing sustained improvements in FEV1 or residual volume (RV) after 6 months. Adverse events included hemoptysis (40 %) and pneumothorax (3.4 %), major complications occurred in 6.9% of cases. Overall survival without lung transplant was 63.8% after 48 months following ELVR, differing insignificantly from what BODE indices of patients would have predicted as median 4-year survival (57%) at the time of ELVR treatment.

Conclusion

Endoscopic lung volume reduction coils can achieve small and short-lived benefits in lung function at the cost of major complications in a highly morbid cohort. Treatment failed to improve 4-year overall survival. ELVR coils are not worthwhile the risk for most patients with severe emphysema.

Introduction

The health burden of chronic obstructive pulmonary disease (COPD) is increasing world-wide [1,2,3]. COPD pathogenesis is triggered mostly be inhaled noxes, e.g. tobacco smoke, causing airway remodeling and

consecutive obstruction. Progressive air trapping leads to the development of emphysema, further deteriorating ventilatory mechanics in COPD patients [4].

While currently available medical therapy helps to attenuate the symptoms, both surgical and endoscopic lung volume reduction (ELVR), apart from lung transplantation, have been proven effective in improving exercise capacity and quality of life [5,6]. However, data about long-term outcome are still rare. ELVR procedures is appealing to many patients due to the seemingly less invasive nature compared to open surgery. Basically, two ELVR treatment modalities are mainly used, endobronchial valves, and coils. Coils are memory-shaped nitol implants, deployed endoscopically in emphysematous areas of the lung. ELVR using endobronchial coils have been shown to improve exercise tolerance, quality of life and lung function[7-9] as compared to optimal medical therapy. Since the introduction of ELVR techniques into clinical routine, our center has collected extensive experience performing both valve- and coil-based ELVR procedures. The aims of this analysis were two-fold:

i) to investigate short- and long-term effects of ELVR on lung function, exercise capacity and all-cause mortality and

ii) to assess the safety of ELVR by implantation of nitinol coils in patients with advanced emphysema in a real-word setting.

Methods

From September 2013 to November 2014, 29 patients received a total of 41 endoscopic lung volume reduction coil implantations. All patients had COPD in advanced stage (spirometrically Global Initiative for Chronic Obstructive Lung Disease; GOLD III or IV) and considerable symptoms despite optimal medical therapy. All patients were screened prior to ELVR by lung function testing and 6-minute walking distance test. Chest computertomography (CT) and ventilation/perfusion (V/Q) scans were analyzed by the interdisciplinary emphysema board (comprising of consultants in radiology/ thoracic surgery/ pneumology) to analyze emphysema distribution and to select target lung lobes suitable for coil placement. The emphysema treatment center has access to intensive care unit beds and extracorporeal lung support at all times.

After patients gave informed consent for the intervention, bronchoscopy and periprocedural preparations were performed according to our internal standard. Nitinol coils were obtained from PneumRX, Inc., Santa Monica, California, USA. The interventionalist placed the bronchoscope at the ostium of the target sub-segmental airway, a catheter was then advanced to measure the distance to the pleura, and the most appropriate coil length (100, 125 or 150mm) based on subsegmental airway length was chosen. Once loaded into the application cartridge, the implanter advanced the coil into the target airway. The endobronchial coil returned to its original shape once fully deployed, thus coiling up the surrounding airway and tensioning the adjacent parenchyma. The goal was to place a minimum of ten endobronchial coils in the target lobe to achieve maximum lung tissue decompression. Coil deployment was done under

fluoroscopic guidance. Twelve out of 29 patients underwent a second procedure on the contralateral side four to six weeks later in the same fashion. Patients were hospitalized for one to three days after coil implantation and discharged when their clinical state was stable. The patients were regularly reassessed on every visit at our outpatient clinic.

Statistical analysis of patients' lung function parameters and 6-MWDs was performed using one-sided t-testing. In case of $p < 0.05$, a difference was considered significant. BODE indices at the time of ELVR treatment were calculated for each patient as proposed by Celli et al.[14] Data on overall survival 48 months after ELVR was collected and Kaplan-Meier-plots were compared to survival data of Celli et al's[14] historic COPD cohort from 2003. Kaplan-Meier-plots were generated using the software Prism 5 (GraphPad Software, San Diego CA, USA).

To exclude that failure to improve a patient's clinical condition was due to misjudgment of the investigator as to which lung lobe should be selected for coil placement, patients' chest CT scans were submitted to two independent commercial providers of CT analysis software and analyses were compared to interventionalist's decision. Program A was provided by PneumRX GmbH (Düsseldorf, Germany, program B was provided by PulmonX, (Redwood City, California). Program A was not deemed specific for coil implantation but was developed rather for the deployment of endobronchial valves.

Results

The patients had a median age of 63.8 years, 65.5% of them were male. Average FEV1 was 0.77 ± 0.3 l before ELVR, mean 6-MWD was 255.5 m ± 142.8 m. All patients had relevant emphysema on their chest CT scan and showed elevated fraction of RV / TLC (mean 71.5 % ± 8.1%) in lung function testing. Six of the 29 patients had previously received valve implantation for endoscopic lung volume reduction, as they had a target lobe according to CT and V/Q-scan without collateral ventilation. **Table 1** provides an overview of patients' baseline characteristics.

Twelve out of 29 patients underwent a second implantation of coils on the contralateral side four to six weeks later to prevent contemporary bilateral pneumothorax.

Between eight and twelve coils were implanted in a single lobe in one session, (average 10.3), most frequently in the right upper lobe (62.1%), followed by the left upper lobe (21.4%). During the second ELVR, the left upper lobe was chosen most frequently (50%) followed by the right upper lobe (25%). The lower lobes were targeted in 13.7% of cases during the first and 25% during the second procedure. The middle lobe was completely neglected.

Two of 29 patients had major complications. Limited hemoptysis was observed relatively frequently following ELVR (40%), one patient required interventional bronchoscopy and intensive care treatment for relevant bleeding. Another patient developed unilateral pneumothorax, which required drainage. Post-interventional pneumonia was not observed. All 29 patients recovered and could be discharged. The frequency of acute exacerbation following ELVR was not recorded.

First and second ELVR (if performed) taken together, coil implantation led to limited short-term improvements in lung function. There was no difference in FEV1 measurable (average increase of 0.04 l ± 0.19 l, p = 0.208). Inspiratory vital capacity (VCin) increased significantly only when first and second intervention were taken into account (increase on average 0.14 l ± 0.39 l, p = 0.032), A significant decrease in RV / TLC was detectable after the first ELVR (mean Δ -2.32% ± 6.24%, p = 0.022). 6-MWD following ELVR did no change significantly (mean Δ -14.03 m ± 73.52 m, p = 0.274). Patients had to take the same number of breaks during testing (mean of 0.76). The amount of oxygen supplemenatation during exercise did not change (mean Δ 0.25 l / min ± 1.14 l / min, p = 0.211) (**Table 2**). Regarding only the second ELVR procedure alone, no relevant improvement of either lung function parameters or 6-MWD were detectable.

At the twelve-month follow-up only few of the mentioned benefits lasted, with FEV1, VC_{in}) and 6-MWD having decreased below patients' performances before ELVR in most cases. In comparison, VC_{in} had decreased by 0.05 l ± 0.44 l, p =0.560 and FEV1 by -0.06 l ± 0.16 l, p = 0.101). While RV / TLC turned out lower than before the procedure, the drop was insignificant (-1.21% ± 12.30%, p = 0.628). After six to twelve months, patients had walked 294.03 m on average during 6-MWD testing, 14.03 m less on average than before ELVR (p = 0.274). **Table 3** provides a summary of relevant long-term outcomes.

The median BODE index of patients immediately prior to ELVR was 5, predicting a 48-month survival rate of 57% [10]. **Figure 1** shows Kaplan-Meier-plots for our study cohort. Three patients received lung transplants during follow-up. Primary outcome was defined as "survival without transplant". Kaplan-Meier-plots reveal a 48-month survival of 63.8%. Comparison to Celli et al's historic COPD cohort [10] revealed no significant difference, implying that ELVC treatment did not increase survival above what would be projected by BODE indices at the time of ELVR.

In order to exclude that failure to improve a patient's clinical condition by ELVR was due to misjudgment of the investigator as to which lung lobe should be targeted for coil placement, patients' chest CT scans were submitted to two independent commercial providers of CT analysis software (A, PneumRX GmbH, Düsseldorf, Germany / B, PulmonX, Redwood City, California). Since both providers required CT slice thicknesses be no more than 1 mm, only 16 out of 29 CTs could be included in the analysis. When target lung lobes were determined by computed algorithms, the selected lobes differed from clinician's choice in 18.75% and 30% of cases, respectively. We therefore checked for any correlation between not-responding to ELVR in any category and software-clinician-mismatch. Patients responded more frequently in 6-MWD (50% vs. 30%) and RV (66.7% vs. 38.5%) but less frequently in FEV1 (33.3% vs. 38.5%) when the investigator had treated a different lung lobe than suggested by software A. The opposite was true for Software B. Patients had benefited less frequently in 6-MWD and FEV1 (40% vs. 33.3% and 57.1% vs. 33.3% respectively) when computed target lobes diverged from investigator's choice. Response in RV in turn was observed more often in case of software-investigator-mismatch (33.3% vs. 16.7%).

Discussion

The main results of this study are: i) the implantation of coils for ELVR does not result in a clinically relevant or sustained benefit for patients with severe COPD and ii) there is no long-term survival benefit after 48 months.

Given current literature, 29 patients can be considered as a relatively large cohort for a single center analysis, as a total of 60 patients were included in a European multicenter randomized controlled trial at the same time and the Swiss National Registry comprises 64 patients treated over a period of three years [11,12]. Since all procedures were performed by the same interventionalist variance in procedure quality is unlikely to have an effect on patient's outcomes. There was no statistically significant overall improvement in either lung function or exercise capacity 6 months after ELVR. Singling out distinct patients, some achieved greater improvements of FEV1, RV and 6-MWD than others. Donohue has previously defined "responders" from ELVR as patients achieving an increase in FEV1 by at least 100 ml [7]. Similar propositions have been made for RV (at least -430 ml) [8] as well as 6-MWD[9] (at least +23 m) and are commonly employed as ELVR response criteria. In this study, 48.3% of patients showed short-term increases in FEV1 of at least 100 mL or more thus potentially qualifying as short-term responders. Response in RV was less frequently observed (31.03%). Only 7 out of 29 patients benefited in both categories. Only 4 out of 25 patients had increases in 6-MWD of more than 26 m (4 patients lost in follow-up), but only two of them also qualified as responders in FEV1 or RV, suggesting that response in lung function

CT scans were submitted to two independent commercial providers of CT analysis software to exclude that failure to improve by ELVR was due to misjudgment of the investigator. When target lung lobes were determined by computed algorithms, the selected lobes differed from clinician's choice in 18.75% and 30% of cases, respectively. Judging from both comparisons, determination of target lung lobes for endoscopic lung volume reduction coils by two commercially available software products was not superior to investigator's choice. Admittedly, one software was not designed to guide coil implantation and the number of properly analyzed CT scans is low, so a definite conclusion if software guided coil deployment is superior to investigator guided isn't possible from the data presented here.

Results from this single-center cohort study indicate that endoscopic lung volume reduction coils did not benefit most patients with severe emphysema. Since most published randomized controlled trials investigating ELVC come to more optimistic conclusions[11,12,13], we first compared the results to the patients' baseline characteristics. The patient populations were very comparable regarding age, sex distribution, body mass index and FEV1[11,12,13], while average forced vital capacity (FVC) and 6-MWD were slightly more severely impaired in our study population. Residual volume as well as RV/TLC on the other hand were quite congruent, indicating that our patient collective mostly represented that of larger RCTs investigating endoscopic lung volume reduction coils. In addition, the number of placed coils per sitting was also 10 on average per procedure. We therefore conclude that a possible beneficial effect was neither disguised by a more morbid cohort, nor by a difference in the procedure itself or the interventionalist's experience.

In May 2019, Slebos et al proposed computed analysis of patients' chest CT scans and RV > 200 % as predictors of response to coils [14]. Interestingly, 60% of long-term responders in our study had baseline RV below 200 % of expected. Additionally, subgroup comparison revealed that response rate was not higher in those cases when investigator's CT analysis overlapped with software-based analysis. We conclude that response criteria as suggested by Slebos et al. did not translate to our study cohort, as they did not identify those patients who ended up benefitting from ELVR.

Comparing the rate of major complications in our study, 6.9% ranked well below what was reported from most above-mentioned clinical trials. It should be noted though that 40% of our patients had hemoptysis to varying degrees post intervention, in one case requiring intensive care. Survival without transplant after 48 months was well comparable to what was predicted by BODE indices, indicating that ELVR coils had no relevant effect on patients' long-term prognosis.

Our study has several important limitations that need to be addressed. The study is a single center retrospective real-life assessment of ELVR using coils. While the baseline parameters of treated patients and primary results of the intervention were comparable to those of other studies, our patients seemed to deteriorate earlier than those of other cohorts. However, we did not compare the results of the intervention to a cohort receiving optimal non-interventional therapy only. Additionally, we did not perform an analysis of the patients' quality of life. This would have been interesting additional information, however, the data had not been consequently collected in this real-world setting for most of the patients.

Another limitation is the fact that some patients did not receive treatment of the contralateral side and six patients had previously received valves, as they had complete lobar fissure without collateral ventilation in a target lobe.

Most importantly, some patients received predominantly coils of 100 mm length, which might have led to less lung tissue compression than what might have been achieved through larger coils. The strategy to implant bigger coils, eventually creating more elastic recoil, was adopted during the study period. However, the impact of coil-size on patient outcome after ELVR is currently unclear.

Conclusion

In this retrospective analysis, ELVR coils led to small and short-lived benefits in lung function and/or exercise capacity in some patients with severe emphysema. Benefits could not be sustained longer than 6 months on average. Response in lung function to ELVR does not adequately correlate to benefits in exercise capacity or quality of life. Given a major complication rate of 6.9% in a highly morbid cohort, we deem the changes induced by ELVR with coils not worthwhile the risk for COPD patients with severe emphysema.

Abbreviations

ELVR – endoscopic lung volume reduction; **EVRC** – endoscopic lung volume reduction coils; **6-MWD** – 6 minute walking distance; **FEV_1** – forced exspiratory volume in one second; **VC** – vital capacity; **RV** – Residual volume; **TLC** – Total lung capacity

Declarations

Ethics approval and consent to participate

The necessity for informed consent was waived for the retrospective, anonymous analysis and publication of the data by the local Ethics Committee (Ärztekammer des Saarlandes). Patients gave written informed consent for the intervention.

Consent for publication

Not applicable

Availability of supporting data

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

Robert Bals received funding from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Grifols, Novartis, CSL Behring, German Federal Ministry of Education and Research (BMBF) Competence Network, Sander Stiftung, Dr. Rolf M. Schwiete Foundation, German Cancer help (Krebshilfe) and Mukosizidose e.V. All other authors declare no conflict of interest.

Funding sources

The study did not receive specific funding.

Authorship Contribution

P.L. performed ELVR interventions, P.L., N.H., H.W., F.L., F.S. and C.L. were in charge of patients follow-up. Data collection and analysis was done by N.H. and P.L., S.M. wrote the manuscript. S.M., F.S. and P.L. drafted the manuscript. H.-J.S. and R.B. revised the manuscript for important intellectual content. All authors have seen and approved the final version of the manuscript.

Acknowledgement

Not applicable.

References

1. Criner RN and Han MK. COPD Care in the 21st Century: A Public Health Priority. Respir Care 2018 May;63(5):591-600
2. Rabe KF and Watz H. Chronic Obstructive Pulmonary Disease. Lancet. 2017 May 13;389(10082):1931-1940
3. López-Campos JL, Tan W, Soriano JB. Global Burden of COPD. Respirology. 2016 Jan;21(1):14-23
4. Tuder RM, Petrache I. Pathogenesis of Chronic Obstructive Pulmonary Disease. J Clin Invest. 2012 Aug;122(8):2749-55
5. Fishman A, Martinez F, Naunheim K et al. A Randomized Trial Comparing Lung-Volume-Reduction Surgery With Medical Therapy for Severe Emphysema. N Engl J Med. 2003 May 22;348(21):2059-73
6. Davey C, Zoumot Z, Jordan S et al. Bronchoscopic Lung Volume Reduction With Endobronchial Valves for Patients With Heterogeneous Emphysema and Intact Interlobar Fissures (The BeLieVeR-HIFi Study): A Randomised Controlled Trial. Lancet. 2015 Sep 12;386(9998):1066-73
7. Shah PL, Zoumot Z, Singh S, et al. Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET): a randomised controlled trial. Lancet Respir Med 2013;1:233-40.
8. Deslee G, Mal H, Dutau H, et al. Lung volume reduction coil treatment vs usual care in patients with severe emphysema: The REVOLENS Randomized Clinical Trial. JAMA 2016;315:175-84.
9. Sciurba FC, Criner GJ, Strange C, et al. Effect of endobronchial coils vs usual care on exercise tolerance in patients with severe emphysema: the RENEW Randomized Clinical Trial. JAMA 2016;315:2178-89.
10. Donohue J. Minimal Clinically Important Differences in COPD Lung Function. COPD. 2005 Mar;2(1):111-24
11. Hartman JE, Ten Hacken NHT, Klooster K et al. The Minimal Important Difference for Residual Volume in Patients With Severe Emphysema. Eur Respir J. 2012 Nov;40(5):1137-41
12. Fellrath JM, Scherer T, Franzen DP, et al. Endobronchial coil therapy in severe emphysema: 6-month outcomes from a Swiss National Registry. J Thorac Dis. 2018 Aug;10(Suppl 23):S2711-S2718
13. Puhan MA, Mador MJ, Held U et al. Interpretation of Treatment Changes in 6-minute Walk Distance in Patients With COPD. Eur Respir J. 2008 Sep;32(3):637-43
14. Celli BR, Cote CG, Marin JM et al. The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease. N Enl J Med. 2004 Mar 4;350(10):1005-12
15. Deslee G, Klooster K, Hetzel M et al. Lung volume reduction coil treatment for patients with severe emphysema: a European multicentre trial. Thorax. 2014 Nov;69(11):980-6.
16. Shah PL, Zoumot Z, Singh S et al. Endobronchial Coils for the Treatment of Severe Emphysema With Hyperinflation (RESET): A Randomised Controlled Trial. Lancet Respir Med. 2013 May;1(3):233-40
17. Deslée G, Mal H, Dutae H et al. Lung Volume Reduction Coil Treatment vs Usual Care in Patients With Severe Emphysema: The REVOLENS Randomized Clinical Trial. JAMA. 2016 Jan 12;315(2):175-84
18. Slebos D-J, Cicenia J, Sciurba FC et al. Predictors of Response to Endobronchial Coil Therapy in Patients With Advanced Emphysema. Chest. 2019 May;155(5):928-937

Figures

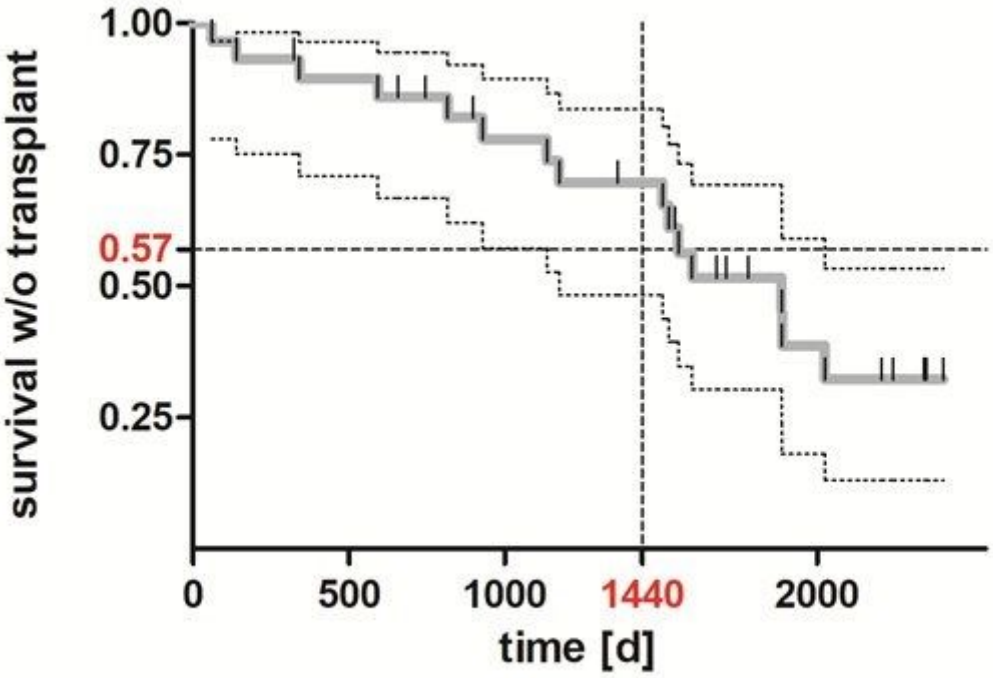

Figure 1

Patients' survival without lung transplant following ELVR - Long-term survival 48 months after ELVR treatment is plotted in a Kaplan-Meier-curve together with a 95% con-fidence interval (CI). Three patients received lung transplant during follow-up. Overall survival without transplant after 48 months was 63.8%. Patients' BODE indices at the time of ELVR predicted an overall survival of 57% after 4 years 10, (marked with dotted lines), which fits well inside the 95% CI of the actual survival curve.