Bronchoscopic lung volume reduction

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CHAPTER

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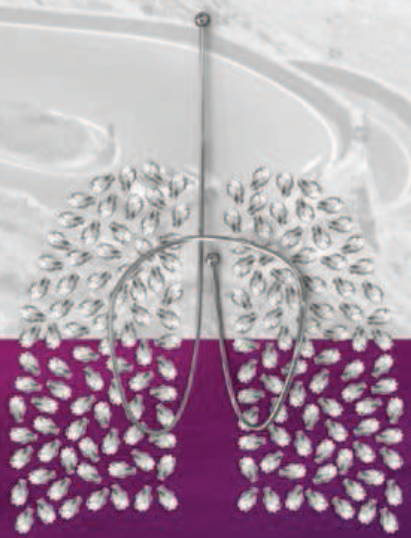

Summary

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The current treatment of COPD offers only limited benefit to patients with severe COPD. A very small subset of these COPD patients will benefit from either lung transplantation or lung volume reduction surgery, but these treatments are highly invasive, scarcely available, and expensive. Therefore, less invasive procedures for lung volume reduction have been developed. In this thesis we investigated two novel bronchoscopic treatments in patients with advanced emphysema; endobronchial valve treatment and lung volume reduction coil treatment.

In **chapter 2** we provide an endoscopic visualization of the rather impressive tissue destruction in the lung parenchyma of a patient with severe emphysema. The alveoli and blood vessels are damaged, and therefore gas exchange is very limited. Furthermore, the lung parenchyma destruction leads to increased tissue elasticity, eventually resulting in increased airway collapse during exhalation, airtrapping and hyperinflation.

In chapter 3 a review (in Dutch) is presented on the current status of bronchoscopic interventions in patients with severe COPD. The review critically appraises the available published data of the coil treatment and endobronchial valve treatment. A case report was added to demonstrate one of our patients who received endobronchial valve treatment. This review was written for a general medical- and non-medical audience to promote, and to better understand these new treatment options for our patients with severe COPD.

In **chapter 4** the results are shown of a study on the role of dynamic hyperinflation in patients with severe COPD. In this study we investigated the feasibility of the manually paced tachypnea test sitting at rest, in 74 patients with severe COPD. We determined the relationship between dynamic hyperinflation and exercise capacity, assessed by the 6 minute walk test. The manually paced tachypnea test was well tolerated in all patients and succeeded to induce dynamic hyperinflation. Multiple regression analysis showed that not dynamic hyperinflation, but static hyperinflation was the most important independent predictor of exercise capacity in this group of patients with very severe COPD.

In **chapter 5** the data of the randomized controlled STELVIO trial is presented. In this study we examined the effectiveness of the endobronchial valve treatment in patients with severe emphysema in whom the absence of collateral ventilation was proven by the Chartis system. Sixty-eight patients 46 female, (mean ± standard deviation age 59±9 years, FEV_1 29±7% of predicted value, forced vital capacity 77±18% of predicted value, and distance on 6 minute walk test 374±86 meter) were randomized to endobronchial valve treatment (N=34) or standard medical care (control group) (N=34). At 6 months, intention-to-treat analyses showed significant between-group differences in favor of the endobronchial valve group in change of FEV_1:+140 ml (95%CI; 55 to 225), forced vital capacity: +347 ml (95%CI; 107 to 588) and in distance on 6 minute walk test +74 meter (95%CI; 47 to 100). By 6 months, 23 serious adverse events were reported in the endobronchial valve group compared to 5 in the control group (P<0.001). One death occurred in the endobronchial valve group. Serious treatment-related adverse events in this group included pneumothorax (18% of patients)

and events requiring valve replacement (12%) or valve removal (15%). This study showed that endobronchial valve treatment resulted in both statistically and clinically significant improvements in pulmonary function, exercise capacity, and quality of life in a selected group of patients with severe emphysema without collateral ventilation. Adverse events needing careful attention did occur, but were manageable.

In the study described in **chapter 6** we investigated the impact of endobronchial valve treatment on physical activity in patients with severe emphysema. Physical activity was measured for 7 days by a triaxial accelerometer at baseline and 6 months follow-up after endobronchial valve treatment, and compared with standard medical care in a randomized controlled trial. Forty-three patients (77% female, age 59±9 years, FEV_1 30±7% of predicted value, steps 3563±2213 per day) wore the accelerometer and were included in the analysis. Nineteen patients received endobronchial valve treatment and 24 standard medical care. At baseline, physical activity level was comparable between groups. After 6 months, the endobronchial valve group improved significantly compared to the controls in steps/day (+1252 versus -148). A greater increase in steps per day was significantly associated with a stronger decrease in residual volume (r=-0.48) and a greater increase in FEV_1 (r=0.41) and in distance on 6 minute walk test (r=0.50). In this study we were able to demonstrate that daily physical activity significantly improved 6 months after bronchoscopic lung volume reduction treatment using endobronchial valves. This improvement was without any specific intervention or encouragement on physical activity.

In **chapters 7, 8, 9** and **10** the development of another new experimental device is shown. In these studies we investigated the bronchoscopic lung volume reduction coil treatment. The first study (**chapter 7**) was a prospective single centre pilot study investigating the feasibility, safety, and efficacy of the coil treatment, specifically in patients with severe heterogeneous emphysema. In this first in human study, 16 patients (baseline FEV_1, 28±8% of predicted value) were treated bronchoscopically with coils under fluoroscopic guidance in 2 sequential procedures. Four patients were treated in 1 lung, and 12 patients were treated in both lungs. A median of 10 (5-12) coils was placed per lung. Adverse events possibly related to either the device or the procedure within 30 days after treatment were pneumothorax (N=1), pneumonia (N=2), COPD exacerbation (N=6), chest pain (N=4), and mild hemoptysis (N=21). From 30 days to 6 months, the adverse events that occurred were pneumonia (N=3) and COPD exacerbation (N=14). All events resolved with standard care. Six months after LVR-coil treatment, there were significant improvements in (mean ± standard deviation) SGRQ, -15±12 points, FEV_1, +15±17%, forced vital capacity, +13±13%, residual volume, -11±9% and distance on 6 minute walk test +84±73 meter (all P<0.005). This study showed that lung volume reduction coil treatment is technically feasible with an acceptable safety profile. We concluded that the lung volume reduction coil treatment is a promising technique for the treatment of patients with severe heterogeneous emphysema.

Following the early experiences of the lung volume reduction coil treatment, we further investigated the feasibility, safety and efficacy of lung volume reduction coil treatment in a multicentre study in a larger group of patients with severe emphysema. **Chapter 8** was based on data of this prospective open-label trial, which was conducted in 11 European hospitals. Sixty patients (61±8 years, FEV_1, 30±6% of predicted value) were bronchoscopically treated with coils (55 bilateral, 5 unilateral), with a median of 10 (range 5–15) coils per lobe. Within 30 days post-treatment, 7 COPD exacerbations (6%), 6 pneumonias (5%), 4 pneumothoraces (4%) and 1 hemoptysis (1%) occurred. At 6 and 12 months, respectively, change in SGRQ was −12±13 points and −11±13 points, change in distance on 6 minute walk test was +30±74 meter and +51±76 meter, change in FEV_1 was +0.11±0.20 Liter and +0.11±0.30 Liter, and change in residual volume was −0.65±0.90 Liter and −0.71±0.81 Liter (all P<0.01). Post-hoc analyses showed significant improvements in SGRQ, 6 minute walking distance and residual volume in patients with both heterogeneous and homogeneous emphysema. This study confirmed our single center open-label study (Chapter 7), showing that lung volume reduction coil treatment results in significant clinical improvements in patients with severe emphysema, with a good safety profile and sustained results for up to 1 year after treatment.

Lung volume reduction coil treatment was shown to be safe and clinically effective in patients with severe emphysema in the short term; however, long-term safety and effectiveness had not been evaluated. Therefore in **Chapter 9**, we further investigated the long-term safety and effectiveness of lung volume reduction coil treatment in patients with severe emphysema. Thirty-eight patients with severe emphysema (median age 59 years, FEV_1 27% of predicted value), who were treated in two previous lung volume reduction coil clinical trials, were invited for a voluntary annual visit. Thirty-five patients visited the hospital 1 year, 27 patients 2 years and 22 patients 3 years following coil placement. No coil migrations were observed on X-ray. At 1-year follow-up, all clinical outcomes significantly improved compared with baseline. At 2 years, residual volume, mMRC score and the SGRQ score were still significantly improved. At 3 years, a significant improvement in mMRC score remained, and 40% of the patients reached the minimal important difference in distance on 6 minute walk test, and 59% in the SGRQ. We concluded that at 3-year follow-up, the lung volume reduction coil treatment showed no long-term unexpected adverse and device-related events.

Lung volume reduction coil treatment has been shown to be effective in patients with heterogeneous emphysema, and our post-hoc results showed a strong signal for efficacy in homogeneous patients as well, but this treatment had not been prospectively investigated in patients with homogeneous emphysema. **In chapter 10** a study is presented that investigated the lung volume reduction coil treatment in severe emphysema patients with a homogeneous emphysema distribution. In this single-arm, open-label study, 10 patients with severe airway obstruction and hyperinflation were treated with a maximum of 12 coils in each upper lobe in 2 sequential procedures. A median of 11 (range 10–12) coils were placed in each lung. Two COPD exacerbations and 1 minor pneumothorax were recorded as serious adverse events. At 6 months, the distance on 6 minute walk test improved from 289 to 350 meter (P=0.005); forced vital capacity from 2.17 to 2.55 Liter (P=0.047); residual volume from 5.04 to 4.44 Liter (P=0.007) and SGRQ score from 63 to 48 points (P=0.028).

This study showed that the benefit of lung volume reduction coil treatment is not limited to patients with heterogeneous emphysema, but that patients with homogeneous emphysema benefit as well.

In **chapter 11** the evolution of the lung volume reduction coil technology and its current status are reviewed. Lung volume reduction coil treatment is a novel therapy, independent of collateral flow, for patients with both heterogeneous as well as homogeneous emphysema. The procedure is feasible, and the treatment has an acceptable safety profile in experienced hands. The efficacy results have shown promising improvements in pulmonary function, exercise capacity and quality of life. Future prospective randomized controlled trial data will have to confirm the efficacy of the lung volume reduction coil treatment in both heterogeneous and homogeneous populations when compared with usual care.