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Two-year results after lung volume reduction surgery in α_1-antitrypsin deficiency *versus* smoker's emphysema

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Two-year results after lung volume reduction surgery in α_1-antitrypsin deficiency versus *smoker's emphysema. P.C. Cassina, H. Teschler, N. Konietzko, D. Theegarten, G. Stamatis. ©ERS Journals Ltd 1998.*

ASBSTRACT: Lung volume reduction surgery (LVRS) improves exercise capacity and relieves dyspnoea in patients with smoker's emphysema (SE). It is unclear, however, whether LVRS similarly improves lung function in α_1-antitrypsin-deficiency emphysema (α_1E).

To address this question, this study prospectively compared the intermediate-term functional outcome in 12 consecutive patients with advanced α_1E and 18 patients with SE who underwent bilateral LVRS. Before surgery there were no statistically significant differences between the two groups in the six-minute walking distance, dyspnoea score, respiratory mechanics or lung function data, except for the forced expiratory volume in one second, which was lower in the deficient group (24 *versus* 31% of the predicted value; p<0.05).

In both groups, bilateral LRVS produced significant improvements in dyspnoea, the six-minute walking distance, lung function and respiratory mechanics. In the α_1E group, the functional data, with the exception of the six-minute walking distance, returned to baseline at 6–12 months postoperation and showed further deterioration at 24 months. The functional status of the SE group remained significantly improved over this period.

In conclusion, the functional improvements resulting from bilateral lung volume reduction surgery are sustained for at least 2 yrs in most patients with smoker's emphysema, but this type of surgery offers only short-term benefits for most patients with α_1E.

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α_1-Antitrypsin deficiency is a hereditary disorder characterized by decreased serum levels of α_1-protease inhibitor (α_1PI), a glycoprotein produced in the liver. α_1PI serves to protect the connective tissue framework of the alveo- lar wall from destruction by proteolytic enzymes, mainly neutrophil elastase. Imbalance between protease and antiprotease activity results in the digestion of connective tissue and predisposes to the development of pulmonary emphysema [1]. A minimum serum level of Š11 μmol·L^{-1} is considered protective against elastase activity [2]. Clinical signs and symptoms of α_1PI-deficiency emphysema (α_1E) usually become manifest after the age of 30 yrs and include dyspnoea, an obstructive ventilatory defect on pulmonary function testing and decreased diffusing capacity for carbon monoxide. Radiographically, α_1PI-deficiency is characterized by panacinar emphysema, with predominance at the lung bases. Treatment includes α_1PI augmentation therapy and symptomatic inhaled bronchodilator therapy [2]. Whether or not the course of the disease is altered by this therapeutic approach is still not proven in controlled clinical studies, although there is some evidence for its efficacy based on comparisons with historical controls [3]. Lung transplantation remains the treatment of choice for selected patients with progressive end-stage α_1E [4].

Lung volume reduction surgery (LVRS), recently introduced as a surgical means of improving functional capacity in patients with heterogeneous smoker's emphysema (SE) [5, 6], is a promising alternative for patients who do not qualify for lung transplantation, because of either age or relevant comorbidity. Whether LVRS has the same potential to improve lung function and alter the course of α_1E as has been demonstrated in SE has yet to be determined [7, 8].

The aim of this study was, therefore, to compare the functional outcome over 2 yrs of follow-up of patients with advanced α_1E and heterogeneous SE who underwent bilateral LVRS at the authors' institution.

Patients and methods

Patient selection

Between March 1995 and November 1996, 12 consecutive patients with severe α_1E (group 1) (seven males, five females, mean±SD age 49±10 yrs) and 18 consecutive patients with heterogeneous SE (group 2) (15 males, three females, mean age 58±11 yrs) were recruited for bilateral LVRS at the authors' institution.

The general selection criteria in both groups were: 1) a severe obstructive ventilatory defect, defined by a forced expiratory volume in one second (FEV1) ð1.1 L and a total lung capacity (TLC) Š120% of the predicted value; 2) Medical Research Council (MRC) dyspnoea score Š2; 3) poor quality of life, as determined by the short form (SF) 36 questionnaire; and 4) radiographic evidence of heterogeneous emphysema with clear target zones for LVRS, absence of bullae >5 cm, and matched ventilation–perfusion scan. Patients were excluded if they continued to smoke, were underweight, defined as a body mass index <18 kg·m^{-2}, had hypercapnia >6.4 kPa, were ventilator–dependent, or had bronchiectasis on computed tomographic (CT) scanning, severe pleural adhesions or coexistent restrictive disease.

All patients in group 1 had α_1E (phenotype PiZZ) with serum levels of α_1PI <11 µmol·L^{-1}. All patients in this group had been receiving weekly supplementation therapy (human α_1PI: 60 mg·kg body weight^{-1}; Prolastin HS®; Bayer, Leverkusen, Germany) for at least 24 months. Supplemental therapy was continued during the perioperative and follow-up periods. Five of the 12 patients with α_1E were exsmokers, in that they had stopped smoking at least 6 months before initiation of replacement therapy, *i.e.* Š2.5 yrs before surgery. In group 2, all patients were recent smokers who had stopped smoking Š2 months before surgery. Based on careful follow-up history and carbon monoxide measurements, none of the patients started smoking again during the two-year follow-up period.

Seven patients in group 1 and 15 in group 2 were receiving oral corticosteroids (ð20 mg·day^{-1} prednisolone). Nine patients in group 1 and 14 in group 2 were using long-term supplemental oxygen either during exercise or at rest.

All patients underwent preoperative evaluation during 3–4 weeks of inpatient cardiopulmonary rehabilitation. The rehabilitation programme included a standardized exercise programme for lower and upper extremities and teaching, including the relevant breathing techniques.

The pulmonary function data at baseline are shown in table 1.

Table 1. – Functional baseline characteristics of the 12 patients with α_1-protease inhibitor (α_1PI)-deficiency emphysema and the 18 patients with smoker's emphysema

Characteristics	α_1PI emphysema (n=12)	Smoker's emphysema (n=18)	p-value
Six-minute walk m	211±103	265±94	0.1
Dyspnoea score	3.2±0.6	3.0±0.6	NS
FEV1 L	0.8±0.3	0.9±0.4	NS
FEV1 % pred	24±7	31±6	NS
TLC % pred	139±20	137±31	NS
FRC % pred	210±37	201±57	NS
RV % pred	342±68	315±81	NS
R_{aw} mbar·L^{-1}·s^{-1}	5.8±1.1	4.2±0.8	0.04
P_{a,O_2} mmHg	65.3±7.1	64.3±5.3	NS
P_{a,CO_2} mmHg	36.8±3.3	38.8±2.1	NS
MIP kPa	4.8±0.4	5.1±0.2	NS
P_{di} kPa	6.0±0.6	6.1±0.4	NS

Values are mean±SD. FEV1: forced expiratory volume in one second; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; R_{aw}: total airway resistance; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; MIP: maximum inspiratory pressure at the mouth; P_{di}: maximum transdiaphragmatic sniff pressure. (1 mbar=0.1 kPa; 1 mmHg= 0.133 kPa.)

Clinical evaluation

The clinical evaluation programme was performed as described in detail previously [9]. All functional baseline data (table 1) were determined after pulmonary rehabilitation during the week preceding surgery. Exercise capacity was assessed by the six-minute walking test. Arterial blood was collected from the radial artery while patients were breathing room air, and blood gas values were measured using an AVL 995 analyser (AVL Medical Instruments, Bad Homburg, Germany). Pulmonary function was measured by standardized body plethysmography (Fenyves & Gut, Bodelshausen, Germany). Maximum inspiratory pressure (MIP) was assessed during forceful efforts initiated at residual volume (RV) against a closed valve, in the sitting position, with a noseclip in place. Maximum sniff transdiaphragmatic pressure (P_{di}) was estimated with an oesophageal and gastric balloon catheter coupled to a pressure transducer, as described previously [9].

Operative technique

A thoracic epidural catheter was placed in all patients to ensure postoperative analgesia. A left-sided double-lumen endotracheal tube (Carlens) was placed to allow single lung ventilation. In patients with SE, LVRS was performed *via* median sternotomy. In the α_1E group, the chest was opened *via* bilateral muscle-sparing anteroaxillary thoracotomy. Median sternotomy for the α_1E group was abandoned after an initial attempt because of technical difficulties encountered with lower lobe mobilization and reduction. The lung with better preserved perfusion was operated on first. With the patient in a full lateral decubitus position, anteroaxillary thoracotomy was performed in the fifth intercostal space after the lung had been deflated. Lung resection was directed to those portions of the lung that remained inflated after 3–5 min of nonventilation (air trapping). It was confirmed that these portions correlated with the findings from CT and radionuclide scans. During LVRS, special care was taken to preserve the lung's natural shape. The staple line was buttressed with bovine pericardium. Pleurodesis or pleural tents were not used prophylactically. The chest was drained using two apically placed tubes and 10 cmH_2O suction. After turning the patient to the contralateral decubitus position, volume reduction of the opposite lung was performed using an identical technique. All patients were extubated in the first hour after surgery and routinely transferred to the intensive care unit for further observation. Chest drain suction was discontinued when the lung had expanded, provided that there was no major air leakage.

Statistical analysis

All data are given as mean±SD, unless otherwise indicated. Statistical analysis was performed using the t-test to

compare the means of normally distributed paired continuous variables and the Wilcoxon's rank sum test to compare continuous non-normally distributed variables. Multiple group comparisons were made using repeated measures of analysis of variance (ANOVA). A p-value <0.05 was considered statistically significant.

Results

Morbidity and mortality

Operation time, including the time required to reposition the patient after completion of surgery of the first side, averaged 146±20 (114–180) min in patients with α_1E and 130±35 (105–200) min in patients with SE (NS). The average duration of chest tube placement was 8±1.5 (6–10) days in patients with α_1E emphysema, compared with 6.5±2 (5–11) days in the SE group (p=0.06). The postoperative duration of hospital stay averaged 18±3 (15–25) days in the α_1E group and 16±4 (14–29) days (NS) in the SE group. All patients were discharged home without chest tubes. There were no hospital deaths in either group, but two patients in the SE group died several months after discharge, one with bronchogenic carcinoma and the other with respiratory failure.

Complications

Postoperative complications included a wound haematoma requiring operative removal in one patient with α_1E and pneumonia in four (33%) patients with α_1E emphysema and in two with SE. The pneumonias were treated successfully with bronchoscopic suction of secretions, vigorous chest physiotherapy and antibiotics. None of the patients required tracheostomy or mechanical ventilatory assistance. Delayed pneumothorax occurred 3–8 weeks after discharge in four patients, three with α_1E and one from the SE group (p<0.05). These patients required repeat thoracotomy because of persistent air leakage after conservative treatment with chest tube drainage had failed. On thoracotomy, severe pleural adhesions were found alongside intact staple lines in these patients. In each of the four patients, a localized leak only a few millimetres from the original suture line at the basilar surface of the lung was demonstrated. The lesions were sutured with 4-zero polypropylene and covered with a pleural tent. The recovery of all patients was otherwise uneventful.

Functional results

The functional results of LVRS in patients with α_1E and SE are shown in table 2 and figures 1 and 2. In patients with severe α_1E follow-up time ranged from 14–29 (median 20) months, with 9 of 12 patients still undergoing measurements at 24 months, while in the SE group the period ranged from 15–32 (median 21) months, with 16 of 18 patients still undergoing measurements at 24 months. Although a number of the subjects did not complete follow-up, the 24-month measurements were included because the longer-term subgroups were not different in any way from the total population. There were no clinically important differences in pulmonary function, respiratory mechanics, or degree of dyspnoea at the initial follow-up visit after 3 months in patients with α_1E and SE. Compared with the preoperative values, all data were significantly improved at this time. In the α_1E group, there was still some benefit after 6 months. By contrast, after 1 yr, the functional data had virtually returned to the preoperative state, except for the six-minute walking distance, which was still slightly improved compared with baseline.

In patients with SE, lung function, respiratory mechanics, six-minute walking distance and dyspnoea score remained improved for at least 1 yr. Trends towards decline in function and performance were seen within the following year after surgery, although most measurements in the SE group were still significantly improved after 2 yrs compared with baseline.

Discussion

The major finding of this study is that the effect of LVRS was short lasting in patients with α_1E. Pulmonary function tests returned to baseline between 6 and 12 months postoperation. LVRS clearly improves pulmonary function and quality of life in patients with end-stage SE in the short term and is associated with relatively low morbidity and mortality [7, 8]. It was unclear from these previous studies, however, whether LVRS improves functional capacity in patients with α_1E, either because they

Table 2. – Follow-up data after bilateral lung reduction surgery in 12 patients with severe α_1-protease inhibitor-deficiency emphysema (α_1E) and 18 patients with smoker's emphysema (SE)

	Baseline		3 months		6 months		12 months		24 months	
	α_1E	SE	α_1E	SE	α_1E	SE	α_1E	SE	α_1E	SE
Patients n	12	18	12	18	12	18	12	17	9	16
Dyspnoea score	3.2±0.6	3.0±0.6	1.8±0.8*	1.6±0.5*	1.9±0.4*	1.5±0.3*	2.2±0.5*	1.7±0.5*	3.1±0.6	2.2±0.5*†
FEV_1 % pred	24±7	31±6†	38±6*	40±6*	34±5*	42±7†	20±6	40±7*†	17±8*	37±6*†
TLC %	139±20	137±31	114±19*	110±14*	134±11*	115±10*†	139±16	119±14*†	145±21*	125±17*†
RV %	342±68	315±81	254±41*	248±25*	291±70*	257±31*	339±65	270±27*†	358±72*	276±28*†
R_{aw} mbar·L^{-1}·s^{-1}	5.8±1.1	4.2±0.8†	4.4±0.9*	3.9±0.5*	4.1±1.0	4.0±1.1	4.9±1.9	4.2±1.4	6.3±2.1*	4.3±1.9†
P_{a,O_2} mmHg	65.3±7.1	64.3±5.3	69±8.5*	69±5*	68±8*	70±5*	63±7	67±8	64±7	65±6
P_{a,CO_2} mmHg	36.8±3.3	38.8±2.1	36.5±5.8	37±2	38±3	38±5	36±3	39±4	36±5	38±3
MIP kPa	4.8±0.4	5.1±0.2	7.3±0.6*	7.8±0.6*	5.6±0.7*	7.9±0.9*†	5.3±0.9	6.5±1*	5.0±0.7	5.8±0.6*
Pdi kPa	6.0±0.6	6.1±0.4	7.7±0.8*	7.9±0.9*	7.2±0.6*	8.3±0.5*†	6.7±0.5	7.5±1.4*	6.2±0.6	7.2±1.2*†

Values are mean±SD. For abbreviations see table 1. *: significantly different (p<0.05) from corresponding baseline; †: significantly different (p<0.05), at given time point from α_1E. (1 mbar=0.1 kPa; 1 mmHg=0.133 kPa.)

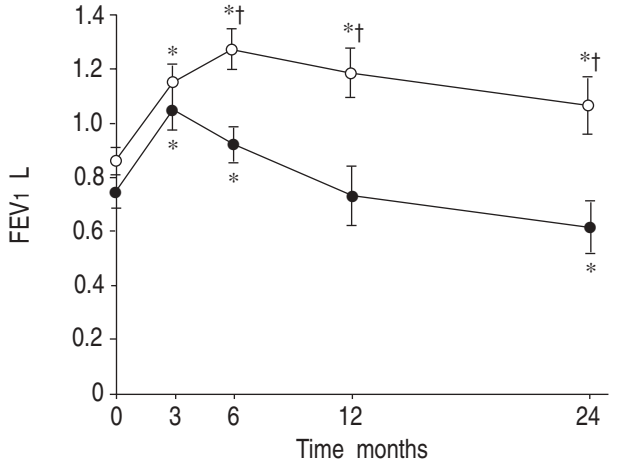

Fig. 1. – Comparison of forced expiratory volume in one second (FEV_1) (mean±SEM) before and on evaluation 3, 6, 12 and 24 months after bilateral lung volume reduction surgery in 12 patients (n=9 at 24 months) with α_1-protease inhibitor-deficiency emphysema (α_1E; ●) and 18 patients (n=16 at 24 months) with smoker's emphysema (❑). *: $p<0.05$ *versus* corresponding baseline; †: $p<0.05$ *versus* α_1E.

were excluded from clinical trials [10] or because their results were not analysed separately from patients with SE [5, 9].

The surgical approach of bilateral thoracotomy in the α_1E group was dictated by the typically basal distribution of emphysema in these patients. After a negative experience with median sternotomy in the first patient, a bilateral, muscle-sparing, anteroaxillary thoracotomy was chosen because it offers a better view of the posterobasal aspect of the lung. In addition, this approach allows performance of multiple wedge resections without applying shearing forces on the lung tissue. Some authors report positive experience with a bilateral thoracosternotomy (clamshell) [11]. However, while extra cross-sternotomy simplifies the procedure, it is not essential. As recently reported [12], a less invasive thoracoscopic approach may also represent a valid alternative to conventional thoracotomy for basally located emphysematous lung, provided that no extensive adhesions are present.

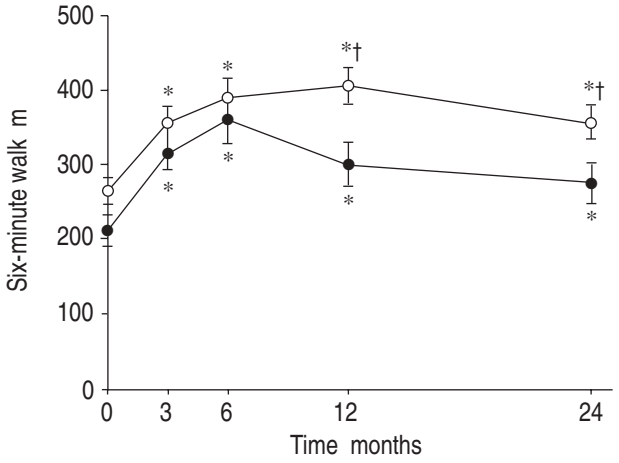

Fig. 2. – Comparison of six-minute walking distance (mean±SEM) before and on evaluation 3, 6, 12 and 24 months after bilateral lung volume reduction surgery in 12 patients (n=9 at 24 months) with α_1-protease inhibitor-deficiency emphysema (α_1E; ●) and 18 patients (n=16 at 24 months) with smoker's emphysema (❑). *: $p<0.05$ *versus* baseline; †: $p<0.05$ *versus* α_1E.

Four cases of delayed pneumothorax were observed, three in the α_1E group and one in the SE group. In two patients, this occurred spontaneously at rest, in another, during exertion and, in the fourth, following a heavy coughing episode. Delayed pneumothorax has been described after laser bullectomy [10] but not after resection with stapling. The higher incidence of delayed pneumothorax may be explained by the more fragile lung tissue and the basal wedge resections with consequent adhesions to the diaphragm, which may cause small parenchymal leaks, especially after extreme exertion or cough.

The functional results of this series demonstrate that LVRS significantly improves the pulmonary function, respiratory mechanics and exercise capacity of selected patients with severe α_1E for up to 6 months. Previous studies in patients with SE have shown that functional improvement is related to 1) the reduction in hyperinflation of the lungs and unloading of the inspiratory muscles [9] and 2) the increase in elastic lung recoil, measured as indicated by an increase in the transpulmonary pressure [13]. In the present study, an improvement in P_{di} and chest wall mechanics was evident from the significant increases in MIP and P_{di} up to 6 months after LVRS. The improvement in elastic recoil is believed to augment the outward traction on the small airways. This is consistent with the observation of significant reductions in airway resistance, residual volume and total lung capacity early after LVRS.

The short-term functional results in the group of patients with α_1E compare well with the authors' own data and with published results after bilateral LVRS in SE. The Washington University Emphysema Surgery Group [5] showed, in their first 20 cases, 3 months after LVRS, an average increase in FEV_1 of 58%, compared with 33% in the present series, and a decrease in TLC of 17%, compared with 19% in the present α_1E patients. These data are also in good agreement with early results reported by other groups after bilateral LVRS *via* median sternotomy [7, 8].

The functional improvement in the patients with α_1E, however, was short lived. Pulmonary function tests returned to baseline 6–12 months postoperatively and showed further deterioration after 24 months of follow-up. Only the six-minute walking distance, after 24 months, continued to be slightly increased over baseline. The observed discrepancy in terms of duration of improvement between spirometric and exercise capacity has also been described in patients undergoing resection of large bullae [14]. The pulmonary function data in the patients with α_1E are in contrast to the excellent two-year follow-up data in the SE group from the authors' centre and to the results recently published by COOPER *et al*. [15] in 150 patients with SE.

One explanation for the rapid functional deterioration could be a technical problem related to the reduction in lung volume. Inadequate resection of lung parenchyma seems unlikely because the short-term results, 3 months after surgery, were satisfactory and of a similar magnitude to those reported previously for SE [7, 16]. The most likely explanations for the observed rapid decline in functional status after the initial improvement are: 1) a more rapid progression of the α_1E in the remaining lung tissue; and 2) impairment of the elevating function of the diaphragm in the zone of apposition caused by progressive adhesions between the diaphragm and chest wall, possibly

induced by LVRS of adjacent basal lung zones and, thus, higher compliance of lung affected by panacinar emphysema [17].

In conclusion, this study clearly shows the importance of the underlying type of emphysema on intermediate-term outcome after bilateral lung volume reduction surgery. In most patients with α_1-protease inhibitor-deficiency emphysema, this type of surgery offers only short-term improvement in lung function, respiratory mechanics and dyspnoea, in contrast to patients with smoker's emphysema, for whom the functional improvement may be sustained for 2 yrs or longer.

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