Interventional Pulmonology

Respiration

Respiration 2014;88:320–328
DOI: 10.1159/000365662

Received: August 17, 2013
Accepted after revision: July 3, 2014
Published online: September 11, 2014

One- to Four-Year Follow-Up of Endobronchial Lung Volume Reduction in Alpha-1-Antitrypsin Deficiency Patients: A Case Series

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Key Words

α_1-Antitrypsin deficiency · Bronchoscopy · Emphysema · Hyperinflation · Lung function · Lung volume reduction · Single lung transplantation

Abstract

Background: Lung volume reduction surgery can improve lung function and working capacity in severe heterogeneous emphysema. Endobronchial lung volume reduction (ELVR) performed by one-way valves inserted via a flexible bronchoscope can result in a moderate but significant improvement in lung function and exercise tolerance, eliminating the surgical risks. ***Objectives:*** Most studies of this method have excluded patients with α_1-antitrypsin (AAT) deficiency, but small series of cases with positive short-term outcome have been reported. The sustainability of results has been questioned and we here present our experience in AAT-deficient patients treated with ELVR followed up for up to 4 years. ***Methods:*** From August 2008 to January 2012, 15 patients were treated with ELVR. Inclusion criteria were homozygotic AAT deficiency, age <80 years, residual volume of 140% or more, forced expiratory volume in 1 s (FEV_1) 15–45% of predicted, severe heterogeneous emphysema, symptoms severely restricting daily life, informed consent and absence of other serious diseases. ***Results:*** One patient coughed up valves after 2 months, 1 developed pneumothorax and had valve displacement and subsequent removal, and 1 improved from an FEV_1 of 0.62 to 0.84 liters, but after 4 months developed repeated and severe pneumonia and the valves had to be removed. Thus, 12 patients remained and were followed up for at least 1 year. In these patients, FEV_1 increased (mean: 54%), the quality of life was much improved, and 2 patients could be taken off oxygen therapy. During the 4-year follow-up, patients demonstrated no significant deterioration in lung function. ***Conclusion:*** In carefully selected AAT deficiency patients with severe emphysema, ELVR can be safely performed with encouraging long-lasting results.

Introduction

Patients with advanced emphysema suffer from reduced lung function, causing severe dyspnea with low oxygen saturation even at minimal exercise, severely reduced working capacity and a low quality of life. Since emphysema is caused by destruction of lung tissue, there

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is no medical treatment. Bronchodilation can be of value if there is a reversible component of the obstruction, and treatment of intercurrent infections is important. Corticosteroids, whether inhaled or oral, are controversial. Long-term oxygen treatment can improve and prolong the life of patients with low oxygen tension in the blood at rest, and rehabilitation can increase the working capacity and improve the quality of life [1], but the lung function is not affected.

The main cause of emphysema is long-term exposure to airborne irritants, especially tobacco smoke. A specific cause is severe α_1-antitrypsin (AAT) deficiency, which predisposes to the early development of emphysema particularly in smokers. It is an inherited disorder, and its severe form is most often related to the ZZ genotype. The prevalence of severe AAT deficiency ranges from approximately 1/2,000 to 1/5,000 based on population screenings [2].

Surgical methods for treating emphysema include lung transplantation and volume reduction surgery. Lung transplantation is costly and carries a substantial surgical risk. Single lung transplantation is most often performed, with an 80–90% 1-year survival and 50–70% surviving 5 years [3], which is not very different from survival with conservative management [4] but with a much better quality of health. Survival after transplantation is, however, improving and has now reached 11 years in Swedish patients with AAT deficiency [5]. The availability of lung transplants is limited, and transplantation is therefore used only in carefully selected patients.

Lung volume reduction surgery (LVRS) was first described in 1957 by Brantigan and Mueller [6]. They claimed that a reduction in the lung volume could improve lung elasticity, and in their series the results were good and long lasting, but the perioperative mortality was high with the surgical and anesthetic methods then available. In the mid-1990s, the method was reintroduced with improved techniques [7]. Randomized studies, such as the large NETT (National Emphysema Treatment Trial) in the United States including 1,218 patients [8] as well as a Swedish study [9], clearly demonstrated that the operation can significantly improve lung function and working capacity, and even reduce mortality in a subset of patients [10].

Still, the perioperative morbidity and mortality rates of LVRS remain considerable, and less invasive methods have therefore been sought. Closure of bronchi with lung sealant [11] or with thermal vapor [12] have been described, but the most investigated method so far is endobronchial lung volume reduction (ELVR). One-way valves are inserted via a flexible bronchoscope into segmental bronchi with the aim of achieving atelectasis of the targeted lobe. Randomized studies have shown a moderate but significant improvement in lung function and exercise tolerance, and a low risk of device- and/or procedure-related complications [13–16]. Improved survival has been seen in patients where atelectasis of the targeted lobe occurred [14]. The method has also been used in the treatment of bronchopleural fistulas with good results [17].

Most ELVR and LVRS studies have excluded patients with AAT deficiency. A small uncontrolled study on such patients followed for 2–12 months after ELVR reported improvement in clinical variables [18]. At our clinic, we have treated AAT deficiency patients using this technique for several years, and results have been favorable in the great majority. We here report the results of the feasibility, efficacy and safety of ELVR in carefully selected patients with AAT deficiency and severe heterogeneous emphysema.

Patients and Methods

This is a retrospective evaluation of all consecutive patients with AAT deficiency treated with ELVR at our clinic. Patients considered to be suitable for the procedure were referred to our department from general practitioners and other clinics, and less than half of those referred fulfilled the criteria. In all, 15 patients were included and received a complete occlusion of the targeted lobe by endobronchial valves.

Criteria for Inclusion

The criteria were homozygotic AAT deficiency, age <80 years, residual volume (RV) of 140% or higher, forced expiratory volume in 1 s (FEV_1) 15–45% of predicted, severe heterogeneous emphysema determined by CT scan and scintigraphy, symptoms severely restricting daily life as described by the patient, informed consent and lack of other serious diseases. Previous single side lung transplantation was not an exclusion criterion if the native lung was severely hyperinflated and thereby compromised the function of the transplanted lung. The target lobe should be clearly hyperinflated and nontargeted lobe(s) must be of a better quality based on CT scan and/or lung scintigram evaluation. In addition, interlobar fissures should be clearly visible and non-interrupted in the CT scan. All patients had received optimal medical treatment (including smoking cessation, vaccinations, long-term oxygen therapy when indicated and bronchodilating therapy) and had undergone physical rehabilitation. The study was approved by the Ethics Committee of the Karolinska Institute.

Baseline Assessment

Clinical examination, lung function tests, chest X-ray, CT scan of the chest in maximal inspiration and expiration with a multislice scanner in axial, coronal and sagittal planes and ventilation

Table 1. Patient characteristics

Patient	Gender	Age, years	BMI	Smoking history (pack years)	Lobe treated	Vents inserted, n	Comments
1	f	59	23.4	Ex- (10)	RLL	3	
2	f	64	23.8	Ex- (30)	LLL	3	
3	m	57	31.0	Ex- (15)	LLL	2	Transplanted unilaterally; lost to follow-up
4	m	49	24.6	Ex- (15)	RLL	3	Coughed up valve after 9 months
5	m	75	21.5	Ex- (14)	LLL	4	LTOT before, not after; died of liver cancer after 3 years
6	m	64	18.9	Never	LLL	2	Accidental death after 2 years
7	m	64	20.1	Never	LLL	3	Improved much initially, but coughed up valves
8	f	72	23.5	Never	ML	1	
9	f	79	20.8	Ex- (20)	LLL	2	Refused spirometry; LTOT before, not after
10	f	68	17.3	Ex- (15)	LLL	2	Transplanted unilaterally
11	f	58	18.9	Never	ML	1	
12	m	59	30.0	Ex- (15)	RLL	3	Immediate infection, valves removed
13	m	75	22.3	Ex- (15)	RLL	3	Improved much initially, but repeated infection necessitated valve removal
14	f	70	21.0	Ex- (10)	LLL	2	Surgery for liver cancer, now pulmonary metastases
15	f	66	23.0	Ex- (20)	RLL	3	

BMI = Body mass index; Ex- = ex-smoker; RLL = right lower lobe; LLL = left lower lobe; ML = middle lobe; LTOT = long-term oxygen therapy.

perfusion scintigraphy were performed. Follow-up assessment was done at 6 months and included clinical examination, lung function tests, chest X-ray and CT scan of the lungs. Thereafter, the patient was seen every 6 months with clinical examination, chest X-ray and FEV_1 measurement. Lobar volume was calculated by manually tracing the fissures in each slice of the targeted lobe and summation of the pixels in the enclosed area and multiplying by the slice thickness and adding all those slices together [19, 20]. This was done before and after the procedure. In each case, the fissures were agreed upon by an experienced clinician and a radiologist.

ELVR Procedure

The most affected lobe was chosen. The patient was sedated with 1–3 mg i.v. of midazolam after premedication according to local guidelines. For bronchial anesthesia, Xylocaine was sprayed. Zephyr® valves (Pulmonx Inc.) were delivered by a dedicated catheter through the working channel of a standard flexible bronchoscope. Both commercially available valve sizes (for bronchial lumens 4–7 and 5.5–8 mm, respectively) were used, with the number and size decided by the anatomy found at bronchoscopy. Only unilateral procedures were performed. No prophylactic antibiotics were given. The Chartis method was not yet available and therefore not used.

Statistical Methods

The distribution of spirometry parameter values was summarized using descriptive statistics. Change in FEV_1 from baseline by visit was assessed using Student's t test for paired samples, with $p < 0.05$ considered to be statistically significant. In addition, 95% confidence intervals for changes in FEV_1 from baseline were calculated.

Results

Patient Characteristics

From August 2008 to January 2012, 15 consecutive patients were included, whereof 2 had severely hyperinflated native lung after single lung transplantation (10 and 18 years earlier, respectively; table 1). Their mean age was 64 years (48–79), body mass index was 21.1 (17.3–31.0), and they had a mean smoking history of 10 pack years. Four were never smokers. All were of the MZZ genotype [tests having been done in Malmö (the Swedish center where patients with AAT deficiency are registered)] and none of the patients had received Prolastin®. The mean FEV_1 was 0.78 liters (25% of predicted), RV 4.87 liters (247%) and the total lung capacity (TLC) 8.88 liters (129%). One to 4 (median, 3) valves were deployed. The procedure lasted less than 30 min and was uneventful. The right lower lobe was targeted in 5 cases, the left lower lobe in 8, and in 2 patients the middle lobe only. In these 2 cases, only 1 valve was needed.

The two unilaterally transplanted patients both had their right lung replaced and their native left lung hyperinflated, and in both the left lower lobe was targeted.

Functional Results

Significant improvements in terms of lung function (tables 2–4) and radiology were observed in most cases. Only

Table 2. Summary statistics for lung function

Parameter	Baseline (n = 15)	6 months (n = 13)	Change vs. baseline, %	1 year (n = 12)	Change vs. baseline, %
FEV_1, liters	0.73 (0.59–1.14)	1.03 (0.65–1.74)	+38	1.13 (0.8–1.63)	+54
FEV_1, % of predicted	26 (18–34)	37 (25–64)		42 (25–80)	
FVC, liters	1.9 (1.2–2.7)	2.6 (1.5–3.9)	+27	ND	
FEV_1/FVC, %	33 (24–55)	41 (29–68)	+24	ND	
RV, liters	4.5 (3.1–10.0)	3.63 (2.5–4.2)	–20	ND	
RV, % of predicted	195 (140–309)	171 (104–230)			
TLC, liters	7.4 (5.9–8.4)	6.9 (5.6–7.7)	–7	ND	
TLC, % of predicted	122 (107–141)	113 (100–130)			
RV/TLC, %	68 (52–81)	54 (60–61)	–21	ND	
Diffusion capacity, % of predicted	28 (25–34)	38 (35–42)	+26	ND	

Arithmetic means (range).

Table 3. Statistical tests for FEV_1 (in liters)

	6 months vs. baseline (n = 13)	1 year vs. baseline (n = 12)	2 years vs. baseline (n = 6)
At baseline	0.776 (0.228)[a]	0.733 (0.172)	0.648 (0.0571)
After treatment	1.06 (0.340)	1.13 (0.394)	1.09 (0.391)
Change vs. baseline	0.288 (0.267)	0.398 (0.415)	0.443 (0.372)
95% CI for change	0.126–0.449	0.135–0.662	0.053–0.834
p value (paired t test)	0.0022	0.0067	0.033

Means (SD).

Table 4. RV before and after the procedure and targeted lobar volume measured by CT (in liters)

Patient	Target lobe	Lobe			FEV_1, liters		RV, liters		
		B[a]	A[a]	decrease	B[b]	A[b]	B[b]	A[b]	decrease
1	RLL	3.5	1.0	2.5	0.7	1.7	6.3	3.9	2.4
2	LLL	1.8	0.5[c]	1.3	0.6	0.7	5.5	4.3	1.2
3	LLL	5.6	–	–	1.1	1.6[d]	–	–	–
4	RLL	2.3	1.3	1.0	0.7	1.0	5.0	3.9	1.1
5	LLL	2.5	1.7	0.8	0.6	0.8	6.0	ND	–
6	LLL	2.8	2.1	0.7	0.9	1.1	5.5	4.8	0.7
8	ML	0.9	0[c]	0.9	0.7	0.8	3.1	2.5	0.6
9	LLL	1.9	1.2	0.7	0.7	1.0	ND		
10	LLL	2.3	0.2[c]	0.9	0.9	1.0	ND		
11	ML	1.6	1.0	0.6	0.6	9.8	6.0	5.1	0.9
13	RLL	3.6	1.8	1.8	1.3	1.5	6.1	3.3	2.8
14	LLL	1.4	0.8	0.6	0.6	0.9	5.8	3.3	2.5
15	RLL	2.9	2.7	0.2	0.7	0.9	4.5	4.7[e]	–0.2

B = Before; A = after; RLL = right lower lobe; LLL = left lower lobe; ML = middle lobe.
[a] Measured by CT. [b] Spirometric measurement. [c] Complete or almost complete atelectasis. [d] Six months after procedure, then lost to follow-up, new CT or spirometry missing. [e] Three months between CT and spirometry.

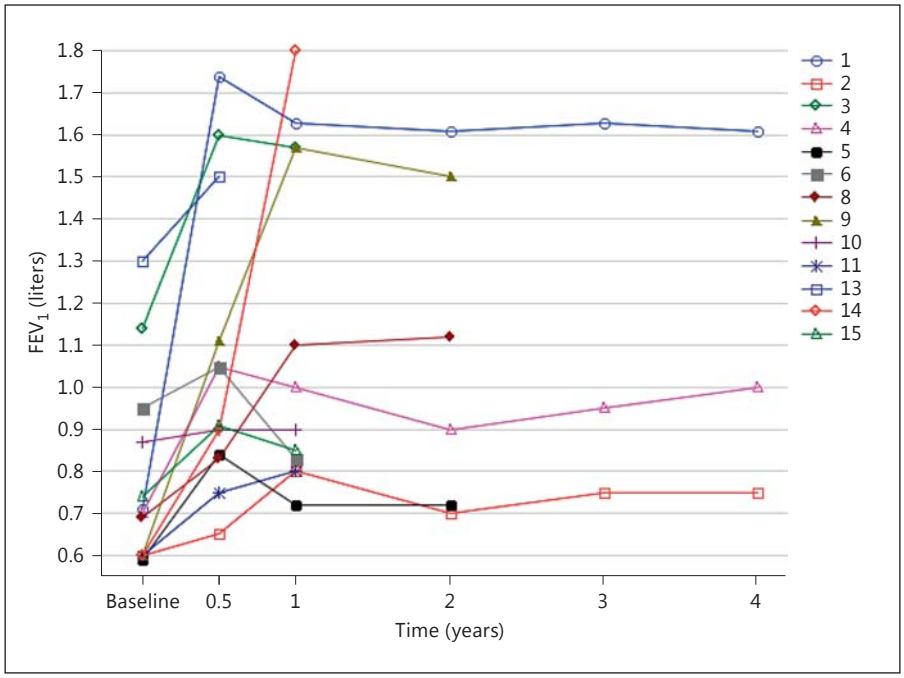

Fig. 1. FEV_1 by visit for patients with data from at least one follow-up (n = 13). Patient numbers are shown.

3 patients achieved complete or almost complete atelectases, but a considerable reduction in size of the targeted lobe was seen the next day in 10 other patients, and this decrease remained during the observation time (except in the patients who had the valves removed or coughed up). FEV_1 at 6 months increased with a mean of 38% and RV decreased with 20%. Two patients were nonresponders, i.e. there was no significant functional or radiological improvement after ELVR. One was one of the earlier transplanted patients, in whom atelectasis of the targeted lower lobe resulted but to no avail, since the upper lobe expanded further, occupying the space previously filled by the lower lobe.

At 1 year, the mean improvement in FEV_1 was even better (54%). This was due to a few patients who had improved considerably (fig. 1). Six have been followed for 2 years and 3 for 3 and 4 years, and lung function was only nonsignificantly worsening and thus much better than before the ELVR procedure (fig. 1).

Of the 4 patients who had long-term oxygen treatment prior to ELVR, 2 no longer needed it.

Complications

One patient developed pneumothorax and upper lobe pneumonia due to valve displacement the day after the procedure. After bronchoscopic removal of the valves and antibiotic treatment, he was back at baseline. Another patient improved from an FEV_1 of 0.62–0.84 liters, but after 4 months developed repeated and severe pneumonias and the valves had to be removed. In 1 patient, valves were coughed up after 2 months. The only other complications were mild hemoptysis resolving during the 1st week (4 patients) and slight non-productive but lasting cough (2 patients). Amongst the remaining 11 patients followed up for at least 1 year, no late complications have occurred.

Three patients died during the follow-up, 1 patient 18 months after the procedure from an accident, 2 after more than 2 years from liver cancer and a heart infarction, respectively.

Two Illustrative Case Reports

Patient 1. One woman was referred at the age of 59 years because of severe emphysema, which restricted her daily life considerably. She could only walk short distances very slowly and had practically no social life. She had smoked 10 cigarettes a day in her youth but had stopped more than 20 years earlier. Radiologically, she had bilateral lower lobe emphysema with the right lower lobe severely hyperinflated and the middle lobe atelectatic (fig. 2). FEV_1 was 0.7 liters (24% of predicted), RV 6.3 liters (309%) and TLC 8.4 liters (141%). The diffusing capacity was 26% of predicted. A lung scintigram revealed that only 30% of the lung function was on the right side, and practically all in the upper part. Three valves were

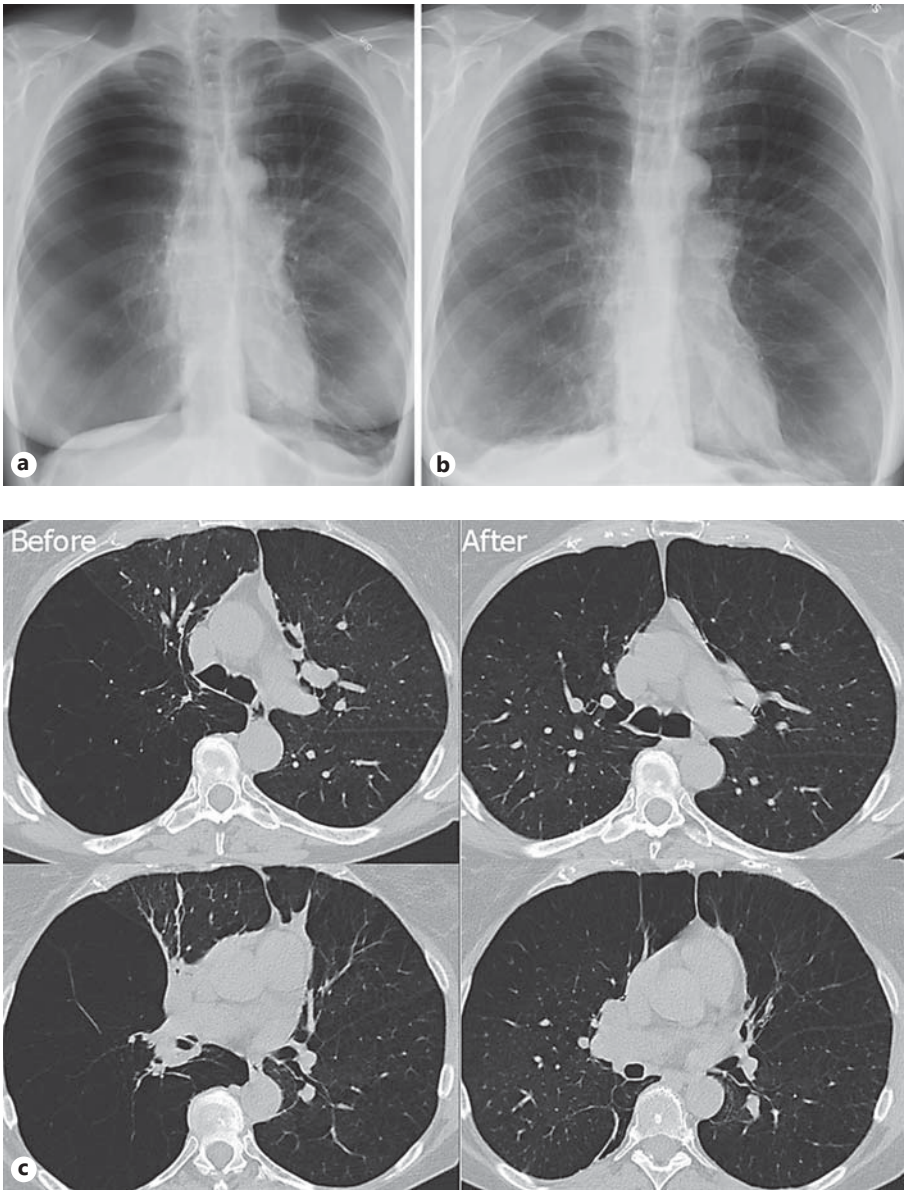

Fig. 2. Patient 1. Chest roentgenogram before (**a**) and after (**b**) ELVR of the right lower lobe. **c** CT slides before (left column) and 6 months after ELVR (right column).

inserted in the right lower lobe, and already the next day the patient was considerably less dyspneic. Radiology showed a remarkable improvement. At 6 months, FEV_1 was 1.7 liters (64%), RV 3.9 liters (130%) and TLC 7.7 liters (130%), and the diffusing capacity was now 46% of predicted. She could now live an almost normal life and had resumed her social life. After 4 years, her FEV_1 amounted to 1.6 liters (58%).

Patient 8. This 71-year-old lady had never smoked. She could only walk up to 100 m very slowly. Radiologically, she had the typical bilateral lower lobe emphysema but most impressive was her hyperinflated middle lobe (fig. 3a). Her lung function showed an FEV_1 of 0.69 liters (29%), RV 3.1 liters (140%) and TLC 5.9 liters (110%). The middle lobe was closed off with 1 valve which caused an atelectasis (fig. 3b). At 6 months, her FEV_1 was 0.8 liters (35%), RV 2.5 liters (115%) and TLC 5.6 liters (104%). Clinically, she improved much. She can now walk at almost normal speed much longer and make her own bed and wash her hair, which had earlier been impossible for her. At 1 year, her FEV_1 had actually increased further to 1.1 liters (48%) and it remained the same at 2 years.

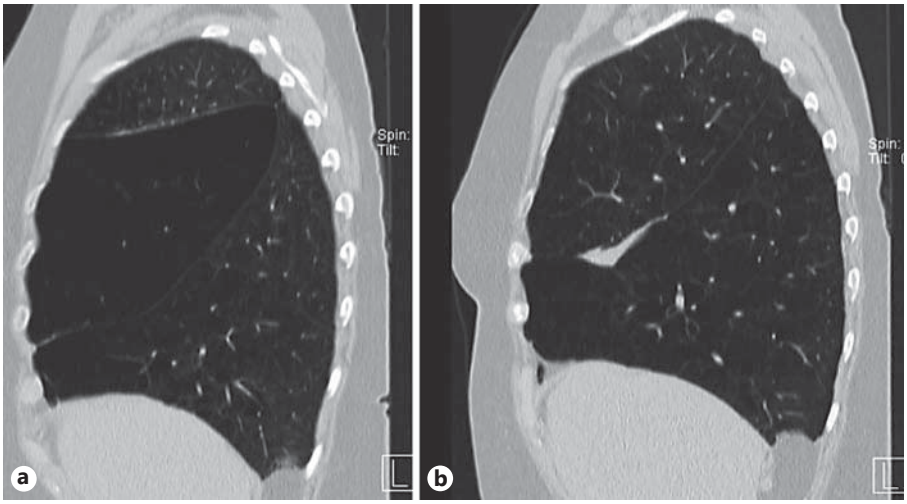

Fig. 3. Patient 8. **a** Sagittal CT scan of the right lung, showing the hyperinflated middle lobe. **b** After ELVR: same view, now an atelectatic middle lobe.

Discussion

AAT deficiency is a hereditary disorder that causes low levels of the enzyme AAT in the blood. AAT is formed in the liver, and the most common genetic defect causes precursors of the enzyme to be deposited there, sometimes causing liver problems such as cirrhosis, which might in turn be a precursor of cancer, which was the cause of death in one of our patients. The most important consequence is, however, a high risk of severe emphysema, which usually develops fairly early in life, especially if the patient has been a smoker. The emphysema is often heterogeneous and typically affects the lower lobes first. In the early LVRS studies, there were some reports that AAT deficiency patients were not suitable for the procedure, possibly because the surgical approach gave best results with upper lobe disease. Since the criteria for ELVR and other nonsurgical methods were taken directly from LVRS studies, such patients were initially excluded from these studies as well. We could see no reason to exclude these patients from ELVR treatment and therefore have included them in our series.

Two factors are of importance for the outcome of ELVR: the degree of emphysema heterogeneity and the presence of collateral ventilation, 'air leakage', between lobes [21]. The goal is to achieve complete lobar atelectasis, which requires completeness of fissures with absence of collateral ventilation. Partial atelectasis is common, which may be sufficient to cause considerable functional improvement [13]. A system to measure the degree of collateral ventilation has been developed and can prevent valve insertion in patients whom it would not benefit [22]. We did not have access to this method, but evaluated the fissures radiologically. The literature confirms that this can be adequate in many instances [23]. The improvement in lung function in the present study seems to indicate that in AAT-deficient patients the fissures are generally much better preserved than in 'ordinary' emphysema patients.

Compared to baseline, patients showed a mean absolute increase in FEV_1 of approximately 400 ml over 1 year (n = 12) and 450 ml over 2 years (n = 6). Calculated as percent of predicted values, FEV_1 increased from 26 to 42% over 1 year ($n = 12$, $p < 0.05$) and from 24 to 42% over 2 years ($n = 6$, $p < 0.05$). In a previous study on ELVR in emphysema patients, the mean absolute FEV_1 increase was 34.5 ml at 6 months and the mean predicted value increased from 30 to 31% [13]. However, in this study, fissures were not studied and thus a considerable number of patients probably did have collateral ventilation, thus considerably weakening the mean effect of the procedure. In a previous study on AAT deficiency patients (n = 6), ELVR resulted in a mean FEV_1 increase of 265 ml measured from baseline to the last available data 2–12 months later [18]. After LVRS, a mean FEV_1 increase of 140 ml 1 year after surgery has been reported [9]. Thus, our results on patients with AAT deficiency compare favorably with those of several other studies in which baseline values for FEV_1 were within similar ranges. In different studies, the yearly rate of decrease in FEV_1 in patients with AAT deficiency has been estimated to be 36–38 ml in never and ex-smokers, increasing to 61–316 ml in current smokers [2]. This effect of the disease should be taken into account when assessing the treatment results in the present study.

Another important finding, as seen from figure 1, is that the improvement in lung function was stable and in most cases seemed to deteriorate only very slowly, giving the responding patients years of a fairly good life. The 3 patients followed for 4 years did not deteriorate significantly over the entire observation period. Good long-term results in patients treated with ELVR have been reporter earlier [24], but to our knowledge not in patients with AAT deficiency. The natural course of this disease is a slow but steady deterioration of lung function, which often will finally necessitate lung transplantation. In our opinion, this outcome could be postponed with ELVR in suitable patients for a number of years. Intravenous augmentation therapy has been shown to affect the lung density change over the years favorably [25], and possibly this could further delay transplantation after ELVR. Some patients might also be eligible for ELVR of the other side after some years.

After unilateral lung transplantation, the emphysematous process might continue in the native lung, which in extreme cases can become so hyperinflated that it compresses the transplanted lung ('native lung hyperinflation'), and LVRS of the native lung can then become necessary [26]. Two of our patients had this problem, and 1 patient improved after ELVR, but the other one did not. As seen from the results in our patients and in accordance with the literature [27], in this situation, ELVR might avoid the risks with LVRS but give similar results. However, if the native lung is extensively destroyed, valves in one lobe might result in an even larger hyperinflation of the remaining lobe(s) and then the patient will not benefit.

We conclude that ELVR in carefully selected AAT deficiency patients with severe emphysema can be safely performed with encouraging long-lasting results. The procedure can easily be reversed if necessary. We therefore believe that ELVR can constitute a bridge to transplantation, i.e. postpone this procedure, presumably for several years.

Acknowledgment

We wish to thank Markus Jerling, MD, PhD, for valuable comments and help with the statistics.

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