Long-term results after lung volume reduction surgery in patients with α_1-antitrypsin deficiency

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Background: The favorable effects of lung volume reduction surgery for selected patients with smoker's emphysema has been demonstrated. However, outcome data for patients with α_1-antitrypsin deficiency emphysema are scarce.

Methods: We prospectively studied pulmonary function, dyspnea, and 6-minute walking distance in 21 patients with severe α_1-antitrypsin deficiency emphysema (*PiZZ* 18, *PiZO* 1, *PiSZ* 2, 10 female patients, median age 56 years, range 38-74 years) for as long as 5 years after thoracoscopic lung volume reduction surgery.

Results: Lung volume reduction surgery improved the mean dyspnea score, from 3.7 $\pm$ 0.1 preoperatively to 1.4 $\pm$ 0.2 at 3 months; the score remained improved for as long as 3.5 years. Mean vital capacity (% predicted) improved from 79% $\pm$ 4.4% to 98% $\pm$ 4.8% at 3 months, and the ratio of residual volume to total lung capacity decreased from 0.67 to 0.51. These improvements lasted for as long as 2 years. The mean airflow obstruction (forced expiratory volume in 1 second % predicted) improved from 27% $\pm$ 1.9% to 38% $\pm$ 3.3% at 3 months and remained statistically improved for 1 year. Four patients showed long-term improvement in lung function for as long as 3.5 years. These patients had markedly heterogeneous emphysema and showed no radiologic signs of airway inflammation.

Conclusions: Lung volume reduction surgery in patients with advanced emphysema from α_1-antitrypsin deficiency results in a significant improvement in dyspnea and lung function for as long as 3.5 years in some cases. It appears that magnitude and duration of these effects are inferior and shorter than those in patients with pure smoker's emphysema. Patients with heterogeneous disease and no or minor inflammatory airway disease may benefit most.

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Lung volume reduction surgery (LVRS) is a successful palliative therapy for carefully selected patients with end-stage emphysema. Several prospective single-center case studies[1-5] and a few randomized, controlled trials[6-11] have shown that LVRS improves lung function, exercise capacity, and quality of life.[12] Only two groups[13,14] have reported on the effect of LVRS in α_1-antitrypsin deficiency emphysema (A1-ATD). In the 12 patients described by Cassina and coworkers,[13] pulmonary function had improved comparably to that seen with smoker's emphysema at 3 months but returned to baseline after 6 to 12 months. In a small group of only 6 patients, Gelb and associates[14] observed variable functional improvements between 2 and 3 years after LVRS. Prospective long-term studies in a larger group of patients have not been published to date. We therefore prospectively studied the course of dyspnea, pulmonary function, and exercise tolerance in 21 patients with A1-ATD emphysema for as long as 5 years after surgery.

TABLE 1. Baseline characteristics of patients with A1-ATD and a matched cohort with smoker's emphysema

	A1-ATD (n = 21)	Smoker's emphysema (n = 21)
Female (No.)	10	9
Age (y)	56 ± 2.0	57 ± 1.8
FEV_1 (L)	0.78 ± 0.04	0.79 ± 0.05
FEV_1 (% predicted)	27 ± 1.9	28 ± 1.9
Residual volume/total lung capacity ratio	0.67 ± 0.02	0.67 ± 0.02
6-min walk distance (m)	278 ± 20	302 ± 19
Medical Research Council score	3.7 ± 0.1	3.43 ± 0.1

Except for numbers of female patients, all data are mean ± SE.

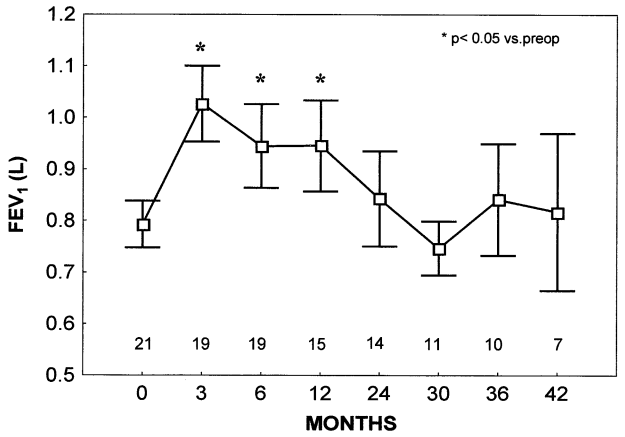

Figure 1. Effect of LVRS on FEV_1 through 42 months. Numbers of patients are given below for each time point. *Squares* represent mean; *error bars* represent SE. *Asterisk* indicates $P < .05$ versus preoperative value.

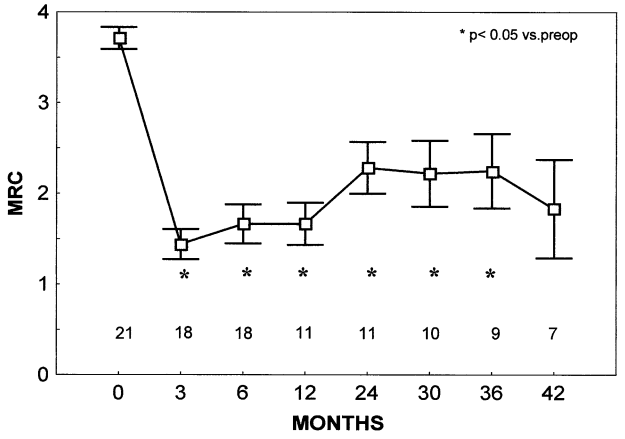

Figure 2. Effect of LVRS on dyspnea, assessed by Medical Research Council dyspnea score, through 42 months. Numbers of patients are given below for each time point. *Squares* represent mean; *error bars* represent SE. *Asterisk* indicates $P < .05$ versus preoperative value.

Material and Methods

Patients

From May 1994 to March 2003, a total of 21 patients with a median age of 56 years (range 38-74 years), with A1-ATD were enrolled in an ongoing prospective trial on the outcome of LVRS[15] that was approved by the ethical committee of our hospital. All patients had severe A1-ATD: 18 patients were homozygous (*PiZZ* phenotype) and 3 were heterozygous (1 with *PiZO* and two patients with *PiSZ*). Two patients (ages 64 and 71 years) were lifelong nonsmokers, whereas the other patients had a smoking history of 20 ± 3.3 pack-years. Only 1 patient had received intravenous α_1-antitrypsin substitution (Prolastin). According to a previously published simple visual chest computed tomographic (CT) scoring system,[16] 13 patients had markedly heterogeneous emphysema, 5 patients had intermediately heterogeneous emphysema, and 3 patients had homogeneous emphysema. The predominant site of destruction was in the lower lobes in 10 cases, in the upper lobes in 4, and in both lobes in 4. In 15 patients moderate inflammatory and postinflammatory changes (of these, 2 patients had bronchiectasis) were visible on the CT scans. We found no difference with respect to a history of infections or exacerbations between these patients and those with pure smoker's emphysema.

Patients were selected for LVRS according to previously published criteria.[17] Twenty-one patients with pure smoker's emphysema with comparable sex, age, and baseline pulmonary function data from our ongoing prospective LVRS study were matched, and their postoperative results were compared with the A1-ATD population (Table 1). However, it was not possible to match these two groups with respect to CT morphology, because the patients with smoker's emphysema had predominantly heterogeneous emphysema with upper lobe predominance.

Surgical Intervention

Bilateral LVRS was performed by video-assisted endoscopic staple (buttressed or not buttressed with bovine pericardium).[18] The lung was resected in areas that showed the most severe emphysema on imaging studies (CT scan and quantitative perfusion scan). In homogeneously destroyed lungs, the site of resection was preferentially chosen in the upper lobes. In 3 patients LVRS was performed only unilaterally because of marked destruction and hyperinflation on one side. Four patients were operated on only in the upper lobes, 10 in the lower lobes, and 7 in both lobes. In 2 patients with complete lower lobe destruction, an anatomic lobectomy was performed. In patients who had a combination of lower and upper lobe destruction, approximately 20% to 30% of the upper lobe was resected, in combination with basilar segments of the lower lobe, and in patients with homogeneous disease, we resected approximately 40% to 50% of both upper lobes. All patients were extubated in the operating room.

Measurements

Pulmonary function studies, including spirometry, plethysmography, and measurements of carbon monoxide diffusion capacity according to the European Respiratory Society criteria[19,20] were performed after the inhalation of 2 puffs of albuterol. Dyspnea was rated with the American Thoracic Society modified Medical Re-

TABLE 2. Outcome after LVRS in patients with A1-ATD emphysema

	Preoperative	3 mo	*P* value	6 mo	*P* value
No. with f/u*	21	19		19	
No. without f/u*					
No. not yet reached f/u					
Cumulative deaths		1		1	
No. transplanted		1		1	
FEV_1 (L)	0.78 ± 0.0	1.04 ± 0.1	.005	0.96 ± 0.1	.01
FEV_1 (% predicted)	27 ± 1.9	38 ± 3.3	.003	34 ± 3.6	.01
IVC (L)	2.89 ± 0.1	3.48 ± 0.2	.0003	3.49 ± 0.2	.004
IVC (% predicted)	79 ± 4.4	98 ± 4.8	.0005	98 ± 5.9	.006
RV/TLC	0.67 ± 0.0	0.51 ± 0.3	.0004	0.53 ± 0.1	.003
DLCO (% predicted)	37 ± 3	40 ± 2	15.8	40 ± 3	8.3
pH	7.4 ± 0.0	7.4 ± 0.0	16.8	7.4 ± 0.0	16.8
$Paco_2$ (mm Hg)	33.8 ± 0.1	36.6 ± 0.2	.09	36 ± 0.2	.09
Pao_2 (mm Hg)	63.6 ± 0.3	65.3 ± 0.3	.04	67.5 ± 0.3	.01
6-min walk distance (m)	278 ± 20	365 ± 20	.01	399 ± 20	.02
Dyspnea (MRC score)	3.7 ± 0.1	1.4 ± 0.2	.0000	1.6 ± 0.2	.0000

Except for numbers of patients, all data are mean ± SE. *f/u,* Follow-up; *IVC,* inspiratory vital capacity; *RV/TLC,* residual volume/total lung capacity ratio; *DLCO,* diffusing capacity of carbon monoxide; *MRC,* Medical Research Council.
*The number of patients with and without follow-up refers to patients alive or free of transplantation.

search Council dyspnea score. For assessment of the 6-minute walking distance, the patients walked along the same hospital hallway without supplemental oxygen. Four patients fulfilled the criteria for long-term oxygen therapy, although they did not receive supplemental oxygen during the 6-minute walk. All measurements were taken within 1 month before LVRS, after 3 months, at 6 months, and then at half-annual intervals.

Data Analysis and Statistics

Values are expressed as mean ± SE. Paired *t* tests and analyses of variance followed by Tukey post hoc test, where appropriate, were performed to detect differences within the same group or between groups.

Results

Morbidity and Mortality

The median duration of hospital stay was 10 days (range 7-13 days). The chest tubes were removed after 6 ± 0.5 days. The most common complication was prolonged air leak (>7 days), which occurred in 7 of 21 patients. One patient needed a reoperation because of a persistent air leak on postoperative day 7. There was no perioperative mortality. During the follow-up, 5 patients underwent lung transplantation (3, 24, 36, 40, and 42 months after LVRS). One patient with unsatisfactory results underwent lung transplantation after 3 months. Three patients died, 2 of respiratory failure (at 24 and 42 months). One patient committed suicide 3 months after surgery despite a good subjective result at that time.

Functional Results

At the time of analysis, patients had reached various time points. The follow-up data are summarized in Tables 2 and 3 for a period extending to 42 months. The mean forced expiratory volume in 1 minute (FEV_1) and Medical Research Council dyspnea score are shown in Figures 1 and 2. The improvements were maximal at 3 to 6 months postoperatively and steadily declined thereafter. Before LVRS, shortness of breath according to the Medical Research Council dyspnea scale was 3.7 ± 0.1; it improved to 1.4 ± 0.2 at 3 months. At that point 85% of patients (n = 16/18) had less dyspnea, which remained for as long as 3.5 years in 6 (of 7 who were alive and free of transplantation). Two patients showed a remarkable increase in FEV_1 (mean FEV_1increased at 3 months after LVRS in 50 %), and two showed a decrease in hyperinflation; both parameters remained improved for as long as 3.5 years after surgery.

Clinical and functional response to LVRS did not statistically correlate with the prospectively assessed emphysema morphologic types, most probably because of the small number. Nevertheless, the 4 patients with the longest lasting functional effects had marked radiologic emphysema heterogeneity; there was marked lung destruction in the lower lobe in 2 patients and in the upper lobe in the other 2, with no radiologic signs of airway or parenchymal inflammation.

Results from gas exchange are shown in Table 2. The mean $Paco_2$ and the mean Pao_2 increased slightly. After 2 years, these findings were no longer present. Four patients fulfilled criteria for long-term oxygen therapy ($Pao_2 \leq 55$ mm Hg) before the operation, whereas at 3 months this was true only for 1 patient.

We found no difference in the functional outcome (Figure 3) between the patients with A1-ATD and a cohort with pure smoker's emphysema matched for age, sex, and function. However, because the two patients groups were not comparable with respect to emphysema morphology (no

12 mo	*P* value	24 mo	*P* value	36 mo	*P* value	42 mo	*P* value
15		14		10		7	
3		2		3		3	
1		1		3		3	
1		2		2		3	
1		2		3		5	
0.95 ± 0.1	.02	0.84 ± 0.1	.26	0.75 ± 0.1	.30	0.82 ± 0.2	.36
34 ± 3.5	.01	30 ± 3.4	.17	28 ± 2.5	.21	31 ± 5.6	.31
3.55 ± 0.2	.003	3.12 ± 0.2	.01	2.63 ± 0.2	.09	2.81 ± 0.3	.77
98 ± 5.7	.008	98 ± 6.7	.005	80 ± 6.1	.09	83 ± 8.3	.89
0.54 ± 0.1	.004	0.57 ± 0.1	.005	0.60 ± 0.1	.43	0.67 ± 0.1	.55
43 ± 4	9.3	42 ± 3	7.0	39 ± 4	3.8	46 ± 5	1.7
7.4 ± 0.0	16.8	7.4 ± 0.0	16.8	7.4 ± 0.0	16.8	7.4 ± 0.0	16.8
36 ± 0.1	.09	36 ± 0.2	.09	36.8 ± 0.2	.09	40 ± 0.2	.06
67.5 ± 0.2	.01	66 ± 0.4	.02	63 ± 0.4	7.0	63 ± 0.4	7.0
406 ± 26	.04	367 ± 26	.09	343 ± 32	1.50	368 ± 53	1.80
1.7 ± 0.2	.001	2.2 ± 0.3	.003	2.57 ± 0.3	.02	1.83 ± 0.5	.01

TABLE 3. Proportion of patients with improvement during follow-up period

Changes	3 mo	6 mo	12 mo	24 mo	36 mo	42 mo
FEV_1 ≥150 mL	10/19	7/19	7/15	4/14	3/10	2/7
Residual volume/total lung capacity ratio ≤0.05	17/19	13/18	12/15	7/13	6/10	2/7
Medical Research Council score ≤1	16/18	17/18	11/11	9/11	7/9	6/7
6-min walk distance ≥50 m	7/18	7/18	5/11	5/11	2/8	2/7

Data are numbers of patients meeting criteria out of patients evaluated. Changes are relative to baseline.

pure smokers with predominant lower lobe emphysema), this comparison is of limited value.

Discussion

Several groups[1,4,5,21,22] have reported long-term results after LVRS in patients with smoker's emphysema. However, in all these reports patients with A1-ATD were either excluded or only included in very small numbers. The natural history and morphology of emphysema in smokers with A1-ATD differ from those of patients with pure smoker's emphysema. Nonsmokers with A1-ATD will not show clinically relevant emphysema before the sixth decade. In smokers with A1-ATD, symptoms of chronic obstructive pulmonary disease generally start at a much earlier age than in patients with pure smoker's emphysema. In addition, A1-ATD preferentially involves the lower parts of the lung, rather than the upper lobes, and is often accompanied by airway inflammation.

Our results demonstrate clinical and physiologic improvements in lung function after LVRS in patients with A1-ATD. We observed an improvement that was maximal at 3 to 6 months and only slightly inferior to the one achieved in pure smoker's emphysema. Thereafter, a relatively rapid decline of the functional gains occurred in many cases, but 4 of the studied patients had long-term response with respect not only to dyspnea but also to lung function. This is approximately 20% of the entire cohort and is quite similar to the durability seen in terms of disease-specific quality of life and exercise capacity in the National Emphysema Treatment Trial.[18] Overall the beneficial effects lasted as long as 2 to 4 years after surgery. These changes were shorter lasting than those observed in patients with pure smoker's emphysema.[18] Of 178 patients who underwent LVRS in our institution and were prospectively assessed for clinical and functional outcome, we selected 21 persons matching the 21 patients with A1-ATD emphysema. A comparison of gain and outcome showed a better result in the group with pure smoker's emphysema, but the results did not differ statistically. This is not surprising, because the two groups are not comparable with regard to morphological severity and distribution of emphysema. Our observations differ from those of others[13] who have reported no beneficial effect present 12 months after LVRS (Table 3). They attribute this poor long-term outcome mostly to in-

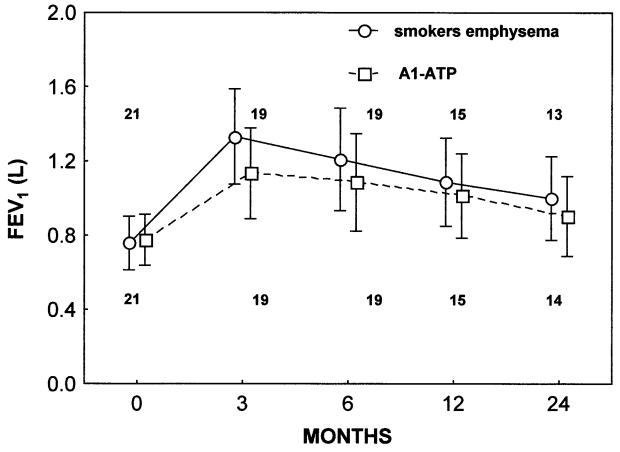

Figure 3. Course of FEV_1 through 2 years after LVRS for patients with A1-ATD *(squares)* and patients with pure smoker's emphysema *(circles).* Numbers of patients are given for each time point, above for patients with smoker's emphysema and below for patients with A1-ATD. *Data points* represent mean; *error bars* represent SE.

flammatory airway changes. This hypothesis is supported by the observation that the 4 patients with long-term responses in our series had, in contrast to the remainder, no indicators of inflammatory disease in the CT scan.

Previously, we and others have demonstrated that emphysema morphologic type is associated with functional outcome after LVRS; that is, patients with heterogeneous emphysema have larger functional improvements than do those with homogeneous disease.[16,23] In this series we were not able to prove such a correlation, most probably because of the small numbers of study subjects. Nevertheless, our 4 patients with long-term responses not only had no signs of airway inflammation but had heterogeneous emphysema with well-preserved pulmonary tissue.

Twelve patients fulfilled the criteria for lung transplantation (age $\leq$60 years, FEV_1 $\leq$25%, no contraindications to transplantation, no preoperative hypercapnea, although 2 were hypoxemic) at the time of LVRS. Of those, 6 patients had an improvement for as long as 3.5 years after LVRS, and transplantation was not necessary. Six other patients successfully underwent lung transplantation.

Despite smaller functional gains and a shorter-lasting effect obtained by LVRS in patients with A1-ATD than in patients with pure smoker's emphysema, LVRS served as a bridging procedure that postponed the need for lung transplantation in most cases. In summary, our data support the contention that patients with A1-ATD should not be excluded from LVRS in all cases. Patients with markedly heterogeneous emphysema and only trivial signs of inflammatory changes on CT scan seem to have the greatest chance for long-term response. In contrast, patients with advanced homogeneous lung destruction and inflammatory airway disease should be preferentially directed to lung transplantation if possible.

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Discussion

Dr Malcolm M. DeCamp, Jr *(Cleveland, Ohio).* One of the most vexing controversies in LVRS is that of patient selection. Tutic and colleagues from Zurich are to be congratulated for tackling this issue in a unique subset of patients, those with emphysema not from smoking alone but from α_1-antitrypsin deficiency.

The strengths of their work are their well-characterized patients with detailed assessments of anatomy, physiology, and function. The weaknesses of this report are the small size of the cohort, the fact that there was no control arm, and the surprisingly variable morphology of these patients despite sharing a deficient genotype.

Only 9 of the 21 patients, just less than 50%, had the classic lower lobe distribution of A1-ATD. That has to be taken into account when we look at these results. More importantly, I think the group elegantly showed that after LVRS there was a disconnection between the measured physiologic benefit, the functional benefit, and the perception of dyspnea. These outcomes deteriorated at varying rates after LVRS.

I have the following questions for Dr Tutic. First, given the variable pattern of emphysema, how do you standardize the video-assisted thoracoscopic resection? Some of these patients had predominantly upper lobe disease, some had lower lobe disease, some had both, and some had diffuse emphysema.

Dr Tutic. Thank you for your questions. Dr Weder will answer them. He is the surgeon who is performing the LVRS.

Dr Weder. Thank you, Dr. DeCamp, for all these questions. First, regarding the morphology and the expected lower lobe predominance of emphysema in patients with A1-ATD, indeed not all the patients operated on showed the typical distribution. This was clearly the case for only half the patients. Additionally, 2 other patients had lower lobe destruction but also some destruction in the upper lobe. Five with what we call intermediate type of heterogeneity had a difference in destruction, but in an area smaller than the size of a segment. Most of them had it in their lower lobe as well, so we are probably talking about approximately 2 thirds of patients with predominance of destruction in the lower lobes.

Now, how did we standardize our surgical procedure? For typical lower lobe disease we either performed a lower lobe resection, which we did in 2 cases, or if we resected the basilar segments, we freed the pulmonary ligament and then started the resection distal to the inferior pulmonary vein, heading more or less horizontally. In patients with a combination of lower lobe and upper lobe disease, of course we resected a piece of the upper lobe as well, and in patients with homogeneous disease, we usually resected in the upper lobe because we believe the shape of the lung is better when the resection is done in the upper lobe.

Dr DeCamp. Along those same lines, how did your operative morbidity, specifically air leak, in this cohort of patients with A1-ATD compare with your previous experience in standard tobacco-induced emphysema LVRS?

Dr Weder. It was slightly better than with smoker's emphysema. We had a 10-day hospital stay and a mean duration of drainage of 6 days, and only a third had more than 7 days of air leaks. One patient was reoperated on because of prolonged air leak.

Dr DeCamp. To get at one of the take-home messages, where you say 30% of your patients have long-term functional benefit, I wonder if you could clarify that. Tell me, of the original 21 patients that you entered into this study, what percentage of them really had functional benefit at 3 years?

Dr Weder. If we include all patients from the beginning, 80% had functional benefit measured by FEV_1, and measured by the Medical Research Council at 6 months, 36% still had a benefit at 3.5 years.

Dr DeCamp. But in your article you talk about 2 of 7 patients.

Dr Weder. Yes, this is correct.

Dr DeCamp. That excludes the deaths and the patients that are transplanted. So with respect to the validity of the statistics, I think it can be somewhat misleading. It's 30% of the surviving, nontransplanted patients that are still benefiting, not 30% of the original cohort.

Dr Weder. Yes, this is correct.

Dr DeCamp. Finally, one of the points that you make very nicely in the article is that for those patients that do benefit, you can forestall the need for lung transplantation as long as 3 years. How would you select a patient who should use LVRS as a bridge, if you will, to transplantation versus a patient for whom LVRS is more futile and should go directly towards transplantation?

Dr Weder. Because we have observed some patients to have really a great benefit at 3.5 years and beyond, we went back to look at all the CT scans again. The individuals who had a long-term benefit showed two characteristics. The first was a clear heterogeneity of the destruction of the lung, with well-preserved lung beside a largely destroyed lung. The second was practically no sign of chronic inflammatory airway disease; they had no bronchiectasis and also no scarring. So I think the patient that you really should consider for LVRS instead of lung transplantation is this type of patient, whereas the other patients who have a relatively advanced destruction of the lung and additionally signs of chronic airway disease should in my opinion be directed to lung transplantation beforehand.