Long-term outcome of bilateral lung volume reduction in 250 consecutive patients with emphysema

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Read at the Eighty-second Annual Meeting of The American Association for Thoracic Surgery, Washington, DC, May 5-8, 2002.

Received for publication July 10, 2002; revisions requested Aug 14, 2002; revisions received Sept 10, 2002; accepted for publication Oct 1, 2002.

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J Thorac Cardiovasc Surg 2003;125:513-25

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0022-5223/2003 \$30.00+0

doi:10.1067/mtc.2003.147

Objective: Numerous reports have confirmed the early benefits of lung volume reduction surgery for selected patients with emphysema. This report documents the long-term survival and functional results after lung volume reduction surgery.

Methods: Between January 1993 and June 2000, a total of 250 consecutive patients underwent bilateral lung volume reduction surgery through median sternotomy at our institution. All patients had disabling dyspnea, thoracic hyperinflation, and a heterogeneous pattern of emphysema with suitable target areas for resection. Preoperative pulmonary rehabilitation was required and post-rehabilitation data were used as the baseline for data analysis. Follow-up ranged from 1.8 to 9.1 years (median 4.4 years).

Results: Prolonged air leaks (>7 days) were the most common complication (45.2%, n = 113). Reexploration rates for air leak and bleeding were 3.2% (n = 8) and 1.2% (n = 3), respectively. Eighteen patients (7.2%) required reintubation and mechanical ventilation. The in-hospital mortality in this series was 4.8% (n = 12). The median length of hospitalization was 9 days (range 4-168 days). Kaplan-Meier survivals after lung volume reduction surgery were 93.6%, 84.4%, and 67.7% at 1, 3, and 5 years, respectively. Eighteen patients (7.2%) have subsequently undergone lung transplantation after a median interval of 4.3 years (range 2.1-6.4 years). Spirometric values, lung volumes, and gas exchange parameters improved after surgery. The forced expiratory volume in 1 second and the residual volume showed statistically significant improvements between preoperative values and each time point of follow-up. Health-related quality of life showed significant postoperative improvement and with time correlated well with the improvement in forced expiratory volume in 1 second.

Conclusions: Lung volume reduction surgery produces significant functional improvement for selected patients with emphysema. For most of these patients, benefits appear to last at least 5 years.

Chronic obstructive pulmonary disease is the fourth leading cause of death in the United States and a leading cause of disability. A variety of treatments, such as smoking cessation, bronchodilators, corticosteroids, and exercise rehabilitation, can improve quality of life for patients with emphysema.^{1,2} Numerous surgical procedures have been proposed to treat emphysema, but only resection of giant bullae and lung transplantation have provided sustained benefit. Four decades ago, Brantigan and colleagues³ suggested that partial pulmonary resection could produce symptomatic and functional improvement in some patients with emphysema. This procedure resulted in high mortality and modest clinical benefit and did not gain wide acceptance. Lung volume reduction surgery (LVRS) was reintroduced by our center in 1993.⁴ Although several large series have reported low operative mortality and significant improvement in the short and intermediate terms,⁵⁻⁸ controversy remains regarding the long-term benefits of this procedure.

Medicare suspended payment for LVRS in 1996 and cosponsored, along with the National Institutes of Health, a long-term randomized trial comparing LVRS with ongoing medical management. The primary outcome was the effect of LVRS on survival relative to control survival. Secondary outcomes included exercise tolerance, quality of life, and measured lung function. Four randomized clinical trials comparing LVRS with ongoing medical management have been published or reported to date.⁹⁻¹² Three of these four have demonstrated benefits of LVRS and have confirmed the progressive decline of the control group, consistent with the known natural history of emphysema. The fourth study, a preliminary report from the National Emphysema Treatment Trial Research (NETT) Group, identified certain high-risk groups within the study that had a high mortality and little benefit.¹² To date there have been limited published data regarding long-term functional outcome.¹³⁻¹⁶ The purpose of this report is to describe the long-term survival and functional results of the first 250 consecutive bilateral LVRS procedures performed at our institution.

Methods

Patient Population

From the outset of our program, a prospective database was maintained for all patients. Data included results of pulmonary function studies, exercise testing, and quality of life assessment. These were obtained at 6 months, at 1 year, and at subsequent yearly intervals whenever possible. A review was conducted from records of the 250 consecutive patients who underwent bilateral LVRS at Barnes Jewish Hospital between January 1993 and June 2000. During this period 50 unilateral LVRS procedures and 35 bullectomies were performed, but these procedures are not included in this report. For the 250 patients studied, the mean follow-up was 4.8 years, with a minimum interval of 18 months.

Follow-up was complete for all patients but 1. Many patients live a long distance from Missouri, and we could not require them to return at fixed intervals. The follow-up data were therefore based on routine appointments and thus could be collected several months before or after the desired follow-up time point.

Details of the selection process have been reported previously.^{17,18} Critical selection criteria are marked hyperinflation of the chest and sufficient regional variation in the emphysema to provide target areas of useless lung accessible to surgical resection. The degree of regional parenchymal destruction is analyzed by standardized computed tomography of the chest, and the regional distribution of function is assessed by radionuclide ventilation-perfusion lung scanning. Thoracic distention is evaluated by chest radiography, and lung volumes are determined by plethysmography. Although the selection process remains subjective in many ways, attempts have been made to identify objective patterns in selection.¹⁹ Inclusion and exclusion criteria are summarized in Table 1.

The on-site evaluation includes physical examination, pulmonary function tests, arterial blood gas analysis (at rest with room air), a 6-minute walk test, and questionnaires assessing quality of life and dyspnea. Fifty percent of more than 800 patients with on-site evaluations were excluded from surgery, and 17% were deferred. The most common reason for exclusion was lack of target areas for surgical resection (76%).

Patients judged suitable for surgery were enrolled in a preoperative pulmonary rehabilitation program, usually for 3 months (median 97 days). Medical therapy was optimized, and dietary regimens were prescribed to adjust body weight to within 20% of the calculated ideal value.

Patients were reassessed the week before surgery with an interval history and physical examination, chest radiography, complete pulmonary function tests, arterial blood gas measurement, 6-minute walk test, and quality-of-life questionnaires. The postrehabilitation, preoperative data were used as the baseline for comparisons with postoperative data.

Pulmonary function tests were performed with a Medgraphics System 1085 (Medical Graphics Corporation, St Paul, Minn) before and after administration of aerosolized albuterol, and the best values for forced vital capacity and forced expiratory volume in 1 second (FEV₁) were chosen for the data analysis. Lung volumes were determined by plethysmography, and diffusion capacity for carbon monoxide (DLCO) was measured by the single-breath technique. During the 6-minute walk test, supplemental oxygen was administered by nasal cannula as needed to maintain the arterial oxygen saturation at 90% or better.

Quality of life was assessed with two self-administered questionnaires, the Nottingham Health Profile²⁰ and the Medical Outcomes Study 36-Item Short-Form Health Survey.²¹ To measure postoperative patient satisfaction, patients were asked to assess their own satisfaction with the operation according to how they felt at the time. There were five possible responses: poor, fair, good, very good, and excellent. All tests were performed during periods of clinical stability.

A complete battery of pulmonary function testing was performed at our institution during the postoperative follow-up periods; an abbreviated battery of tests (FEV₁ and residual volume [RV]) from other institutions was also used. Follow-up evaluation

TABLE 1. Guidelines for evaluating patients for LVRS

	Inclusion criteria	Exclusion criteria
General	Disability despite maximal rehabilitation Cessation of tobacco use >6 mo Patient expectation of goals reasonable	Inability to participate in rehabilitation Continued use of tobacco Significant comorbidity Previous pleurodesis or thoracotomy Underweight, overweight
Anatomic radiographic evaluation	Marked emphysema Heterogeneously distributed emphysema Target zones of poorly perfused lung Areas with better preserved lung Marked thoracic hyperinflation	Bronchiectasis Minimal radiographically evident emphysema Homogeneously distributed emphysema No target zones No preserved lung tissue Chest wall or thoracic cage abnormalities
Physiologic evaluation	Marked airflow obstruction Marked hyperinflation Alveolar gas exchange DLCO <50% Cardiovascular function Essentially normal ejection fraction	Minimal to moderate airflow obstruction Minimal to moderate thoracic hyperinflation Markedly disordered alveolar gas exchange DLCO <10% Paco ₂ >60 mm Hg Cardiovascular dysfunction Left ventricular ejection fraction <40% Mean pulmonary artery pressure >35 mm Hg Significant coronary artery disease

also included arterial blood gas measurement on room air, 6-minute walk test, and completion of questionnaires assessing dyspnea and quality of life.

Surgical Technique

All procedures were performed through a median sternotomy, except one that was done through a bilateral muscle-sparing thoracotomy because of a previous sternotomy for coronary bypass surgery. The operative technique has evolved little since our initial experience. Initially, successive applications of the stapler produced an inverted U-shaped line of excision, from the medial aspect of the right upper lobe towards the apex and down the posterolateral aspect. Now the line of excision from the horizontal fissure is carried straight toward the posterolateral aspect of the right upper lobe, almost completely removing the entire lobe. The same procedure is then repeated on the left, where the upper portion of the upper lobe is excised, leaving only the lingula in place. The transition has been gradual and subtle; therefore there is no ability to distinguish patients retrospectively with regard to the style of stapler application. In 19 patients with lobar destruction and complete fissures, an anatomic lobectomy was performed rather than wedge excisions. When a residual space remained at the apex of the chest at the end of the procedure, we often created a pleural tent to allow the apical pleura to drop down to the upper surface of the remaining lung. Two chest tubes were placed on

either side. The pleura was closed bilaterally before closure of the sternotomy. The chest tubes were brought out through the upper abdomen in a subxiphoid position.

All patients were extubated in the operating room or shortly thereafter in the postanesthesia recovery area. One patient required immediate reintubation and spent the night with ventilatory support, with successful extubation the next morning. The surgical and anesthetic techniques have been previously described elsewhere.^{4,5,22}

Postoperative Management

Our standard postoperative management has been previously described elsewhere.⁵ Adequate postoperative pain relief was facilitated by the use of continuous analgesia through a thoracic epidural catheter positioned with its tip at the T4 level. This eliminated the need for intraoperative systemic narcotics and provided optimal postoperative pain management with minimal respiratory depressants.

On the first postoperative day, use of a bedside treadmill supplemented the efforts of experienced physiotherapists and thoracic surgical nurses to provide vigorous chest physiotherapy and ambulation. Despite this intensive program, minitracheostomy (Cook Cricothyrotomy Catheter, Cook Inc., Bloomington, Ind) for tracheal suction was frequently used for patients with thick secretions and feeble coughs.

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TABLE 2. Pulmonary function and exercise test results before and after surgery

	Evaluation baseline (n = 249)	After rehabilitation (n = 249)	6 mo PO (n = 231)	1 y PO (n = 225)	3 y PO (n = 178)	5 y PO (n = 106)
Time from surgery (d, mean $\pm$ SD)	-124 $\pm$ 79	-6 $\pm$ 5	193 $\pm$ 36	401 $\pm$ 60	1076 $\pm$ 133	1799 $\pm$ 217
FEV ₁						
Mean $\pm$ SD (L)	0.7 $\pm$ 0.2	0.7 $\pm$ 0.3	1.1 $\pm$ 0.5	1.0 $\pm$ 0.5	0.9 $\pm$ 0.5	0.8 $\pm$ 0.5
% predicted	25%*	26%	39%†	38%†	34%†	30%‡
RV						
Mean $\pm$ SD (L)	5.9 $\pm$ 1.4	5.8 $\pm$ 1.3	4.0 $\pm$ 1.2	4.1 $\pm$ 1.3	4.2 $\pm$ 1.3	4.8 $\pm$ 1.8
% predicted	282%*	277%	189%†	193%†	198%†	222%†
RV/total lung capacity (%; mean $\pm$ SD)	72 $\pm$ 7*	70 $\pm$ 7	57 $\pm$ 9†	58 $\pm$ 10†	61 $\pm$ 11†	66 $\pm$ 11†
DLCO						
Mean $\pm$ SD (mL/[min $\cdot$ mm Hg])	9.1 $\pm$ 3.7	8.9 $\pm$ 3.9	10.4 $\pm$ 4.6	10.3 $\pm$ 4.3	9.2 $\pm$ 4.1	8.6 $\pm$ 4.2
% predicted	34%*	33%	39%†	39%†	36%*	34%*
6-min walk (mean $\pm$ SD, ft)	919 $\pm$ 335†	1142 $\pm$ 291	1345 $\pm$ 316†	1341 $\pm$ 310†	1271 $\pm$ 305†	1154 $\pm$ 348*

PO, Postoperative.

* $P \geq .05$ for paired analyses with scores after rehabilitation.† $P \leq .001$ for paired analyses with scores after rehabilitation.‡ $P .02$ for paired analyses with scores after rehabilitation.

Statistical Analysis

Descriptive statistics are expressed as mean $\pm$ SD unless otherwise specified. Categorical data are expressed as counts and proportions. Comparisons were done with paired, two-tailed t tests for means of normally distributed continuous variables and Wilcoxon rank sum tests for skewed data. Either χ^2 or Fisher exact tests were used to analyze differences among the categorical data. Kaplan-Meier estimation was used to depict survival.

Cox multivariate proportional hazards regression was used to identify risk factors for death after LVRS. The time to death was selected as the principal outcome. The regression models were constructed with dependent variables known or suspected to be independent predictors of survival on the basis of previous published results and the univariate differences observed between our subgroups. The following categorical variables were considered: gender, distribution of disease (upper vs lower lobe predominance), patients with both a preoperative FEV₁ and DLCO percent predicted of 20% or less compared with the remaining patients, and preoperative Paco₂ measurement stratified as 50 mm Hg or less versus more than 50 mm Hg. The following continuous variables were considered: age in years, preoperative FEV₁ in liters, RV in liters, DLCO in milliliters per minute per millimeter of mercury, and 6-minute walk test in feet. All data analysis was performed with Systat (Systat 10.0 for Windows; SPSS Inc, Chicago, Ill).

Results

Baseline

The mean age was 62 $\pm$ 8 years. All patients were former smokers, and 50% were female. As expected, most patients (n = 229) were seen with the major focus of disease in the upper lobes; however, the most severe destruction was in the lower lobes in 21 patients (8.4%), including 12 patients (4.8%) with known α_1 -antitrypsin deficiency. Preoperative pulmonary function, 6-minute walk data, arterial blood gas values, and oxygen supplementation requirements of all

patients who underwent bilateral LVRS are depicted in Tables 2 and 3.

Hospital Course

The 90-day and complete in-hospital mortalities in this series were 4% (n = 10) and 4.8% (n = 12), respectively. All early postoperative deaths were attributed to respiratory failure, except 1 that was attributed to pulmonary embolism (Table 4). There were no intraoperative deaths.

Prolonged air leaks (>7 days) were the most common complication (45.2%, n = 113). Reexploration rates for air leak and bleeding were 3.2% (n = 8) and 1.2% (n = 3), respectively, and reexplorations occurred more frequently early in the series. Eighteen patients (7.2%) required reintubation at some time during the hospital stay. Ten of these patients progressed to require a tracheostomy, and 8 were extubated. All patients were weaned from mechanical ventilation before discharge. Other operative morbidities are listed in Table 4. The median length of hospitalization in the survivors was 9 days (range 4-168 days). A minitracheostomy was placed in 43 patients (17.2%), either in the operating room or later at the bedside.

Follow-up Information

Follow-up ranged from 1.8 years to 9.1 years (median 4.4 years). Only 1 patient was unavailable for follow-up. Ninety-six (38.4%) of 250 patients have died, most (65.6%) of respiratory failure.

The Kaplan-Meier estimate of survival at 5 years after LVRS was 67.7% (n = 108), as shown in Figure 1. Eighteen patients (7.2%) have subsequently undergone lung transplantation after a median interval of 4.3 years (range 2.1-6.4). All 18 of these patients survived the initial posttransplantation hospitalization.

TABLE 3. Alveolar gas exchange and oxygen supplementation before and after surgery

	Evaluation baseline (n = 249)	After rehabilitation (n = 249)	6 mo PO (n = 231)	1 y PO (n = 225)	3 y PO (n = 178)	5 y PO (n = 106)
Paco ₂ (mm Hg)	42 ± 6	42 ± 6	39 ± 5	39 ± 5	42 ± 6	42 ± 6
Pao ₂ (mm Hg)	64 ± 9	64 ± 9	72 ± 10	72 ± 11	72 ± 13	69 ± 11
Supplemental oxygen						
Required continuously (% of patients)	60.8%	44.8%	11.3%	12.4%	15.2%	22.6%
Required during exercise (% of patients)	83.6%	91.6%	50.2%	56.4%	70.1%	80.0%

PO, Postoperative.

Functional Results

Pulmonary function test results are shown in Table 2. More than 95% of evaluable patients had objective pulmonary function information available at each follow-up period. Spirometric parameters, lung volumes, and gas exchange improved after surgery. The FEV₁ and RV showed statistically significant improvements between preoperative values and each time point of follow-up. There were no statistically significant differences between initial evaluation and postrehabilitation FEV₁ and RV. Six months after the operation, FEV₁ had increased in 94% of patients; the mean change from preoperative values was 54%. After 5 years, the mean change in FEV₁ was an improvement of 7%, and 53% of patients still had an increase relative to the preoperative value. Six months and 1 year after the operation, RV had declined by 30%, and 90% of patients showed improvement. At 5-year follow-up, 79% of patients still showed an improvement, and the mean RV showed a decrease of 14% from the preoperative value.

The DLCO data showed a 25% increase from preoperative values on follow-up at 6 months and 1 year. At those time points, 67% of patients had improvement with respect to baseline. At 3 and 5 years, the difference did not reach statistical significance, but at 5-year follow-up there was still an average of 7% of increase from preoperative value, with 53% of patients showing improvement.

Results from gas exchange and oxygen supplementation requirements are shown in Table 3. The mean Pao₂ had increased by 8 mm Hg at 6-month, 1-year, and 3-year follow-ups and by 5 mm Hg at 5 years. Seventy-nine percent of patients showed improvement at 3 years, and 66% still did so at 5-year follow-up.

Supplemental oxygen requirements at rest substantially declined after the operation (45% vs 12%, 15%, and 22% at 1, 3, and 5 years, respectively). Before the operation, 92% of patients required supplemental oxygen with maximum exertion. At 6 months, 1 year, and 5 years, the percentages were 50%, 56%, and 80%, respectively.

Functional improvement was also measured by the 6-minute walk test, and results are shown in Table 2. There

TABLE 4. Hospital course data for first 250 consecutive patients undergoing LVRS

Event	Frequency (n = 250)	
	No.	%
Morbidity	138	55.2
Prolonged air leak (>7 d)	113	45.2
Pneumonia	24	9.6
Reintubation	18	7.2
Tracheostomy	10	4
Small bowel obstruction or ileus	6	2.4
Myocardial infarction	5	2.0
Deep vein thrombosis	4	1.6
Cecal perforation	2	0.8
Phrenic nerve injury	2	0.8
Subsequent operation	18	7.2
Reexploration		
Prolonged air leak	8	3.2
Bleeding	3	1.2
Gastrointestinal complication	6	2.4
Coronary artery bypass grafting	1	0.4
In-hospital mortality	12	4.8
Hospital stay of survivors (d)		
Median		9
Range		4-168

was a significant improvement in physical ability during the preoperative rehabilitation period. There was a further increase in performance after the operation. This improvement was maintained for 3 years, followed by a gradual decline. Exercise tolerance scores after 5 years were not worse than preoperative scores.

The Medical Research Council Dyspnea Scale showed a reduction of dyspnea at 6 months, when 88% of patients reported improvement (Figure 2). These improvements were sustained through the 1-year follow-up period, when 79% of patients were still showing improvement, 18% had no change, and only 3% showed worsening. At 5 years after the procedure, only 20% of patients reported a worse score.

Health-related quality of life, according to the SF-36 Physical Functioning (PF) Scale scores, showed marked

Figure 1. Kaplan-Meier survival graph after LVRS. Data were censored for missing data (1 patient), lung transplantation (18 patients), or end of follow-up.

Figure 2. Respondent score changes in Modified Medical Research Council Dyspnea Scale after LVRS.

improvement relative to that reported by the same patients after rehabilitation but before the procedure (Figure 3). At 6 months, 1 year, 3 years, and 5 years after the operation, 97%, 96%, 93%, and 92% of the evaluable patients, respectively, responded to the SF-36 PF questionnaire. The SF-36 PF questionnaire is scored on a scale of 100, with 0 being the worst and 100 being the best. Before the operation, the mean baseline score was 18, indicating very severe limitation. The score peaked at 58 points at 6 months, and after 5 years almost 80% of patients still reported improvement relative to their own baseline scores. One subsection of the SF-36 PF Scale asks the patient to compare his or her health with that 1 year earlier. Ninety-six percent of patients felt better at 6 months after the operation, and almost 88% did so at 1 year.

When asked to assess their own satisfaction with the operation, 97% of patients reported good or excellent overall satisfaction 6 months after the procedure. At 5 years, only 18% reported poor or fair satisfaction (Figure 4).

Longitudinal data with a shrinking cohort of observable patients are prone to bias. To try to dissect out the role of dropouts as a result of death, we separately analyzed data from the cohort of patients with complete data at all time points out to 5 years (Table 5). These data were comparable to the data from the overall data pool (Table 2). Both demonstrated that on average half of the initial improvement in FEV₁ was lost at 3 years, with a return to the baseline value at 5 years. Thus there is no evidence that the mean values obtained late in follow-up were inappropriately elevated by the dropping out of the lower values. For the

Figure 3. SF-36 PF Scale scores from before LVRS (baseline) and after surgery.

Figure 4. Postoperative patient overall satisfaction.

5-year cohort, the health-related quality of life scores according to the SF-36 PF analysis at each time point were essentially the same as in the overall analysis of the follow-up data for all patients.

To better assess our selection criteria, we separately analyzed results achieved in patients for whom LVRS has been especially controversial. This group included patients with lower lobe destruction and those with the most severely impaired lung function, specifically those with both FEV₁ and DLCO values 20% or less of predicted values.

Twenty-one patients in this cohort had predominantly lower lobe destruction and underwent bilateral lower lobe LVRS. Of these, 12 had α_1 -antitrypsin deficiency. Results of the lower lobe group are compared with the upper lobe resection group in Table 6. The 6-month results of the two groups were similar, but thereafter the loss of function in the lower lobe group appeared to occur at a much higher rate

than that seen in the upper lobe group. The mean FEV₁ at 5 years in the lower lobe group was below the baseline value, whereas the mean FEV₁ in the upper lobe group remained 9% above the baseline value. A similar accelerated rate of decline for the lower lobe group was observed in the 6-minute walk distance.

Patients with both a low FEV₁ and a low DLCO ($\leq 20\%$ of predicted) have recently been identified by the NETT study as being at high risk in undergoing LVRS. The NETT interim report suggests excessive early mortality and poor functional outcome.¹³ Twenty such patients (8%) were identified in this series, and the results in this group are shown in Table 7. The initial improvements in both FEV₁ percentage and 6-minute walk test for the high-risk group exceeded those for all other patients. Furthermore, the high-risk group of patients showed a larger improvement in DLCO at 6 months than did all other patients (70% vs 21% improvement).

TABLE 5. Change in function with time for a cohort of patients with complete data

	After rehabilitation	6 mo PO	1 y PO	3 y PO	5 y PO
FEV ₁ (n = 95)					
Mean ± SD (L)	0.75 ± 0.1	1.17 ± 0.1	1.08 ± 0.2	0.92 ± 0.3	0.81 ± 0.1
% predicted	26%	41%	38%	33%	30%
RV (n = 75)					
Mean ± SD (L)	5.8 ± 1.0	3.9 ± 0.8	4.2 ± 0.9	4.2 ± 0.9	4.8 ± 1.0
% predicted	276%	183%	195%	194%	210%
DLCO (n = 70)					
Mean ± SD (mL/ [min · mm Hg])	9.4 ± 3.5	11.4 ± 4.1	11.5 ± 4.3	10.0 ± 4.1	9.2 ± 4.0
% predicted	33%	42%	43%	38%	33%
6-min walk (ft, mean ± SD, n = 93)	1177 ± 243	1470 ± 375	1408 ± 278	1309 ± 317	1159 ± 316
SF-36 PF Score (mean ± SD, n = 88)	18 ± 6	66 ± 16	61 ± 12	46 ± 16	33 ± 13

Numbers of patients are those with selected outcome variables that were measured at every time point. PO, Postoperative.

TABLE 6. Subgroup analysis of pulmonary function and exercise test results before and after surgery between patients with predominately lower lobe distribution of disease and those with predominately upper-lobe distribution

	After rehabilitation	6 mo PO	1 y PO	3 y PO	5 y PO
Lower lobe (n = 21)					
FEV ₁					
Mean ± SD (L)	0.65 ± 0.2	1.01 ± 0.6	0.75 ± 0.3	0.72 ± 0.3	0.59 ± 0.2
% predicted	22%	30%	27%	26%	21%
% change*	NA	54 ± 69	18 ± 31	14 ± 49	-14 ± 23
6-min walk					
Mean ± SD (ft)	1210 ± 230	1450 ± 405	1315 ± 379	1338 ± 295	1240 ± 361
% change*	NA	19 ± 32	9 ± 28	9 ± 28	7 ± 28
Kaplan-Meier survival	NA	100%	95.2%	79.8%	59.9%†
Upper lobe (n = 229)					
FEV ₁					
Mean ± SD (L)	0.72 ± 0.3	1.10 ± 0.5	1.07 ± 0.5	0.92 ± 0.5	0.84 ± 0.5
% predicted	26%	40%	39%	34%	31%
% change*	NA	54 ± 42	49 ± 48	26 ± 41	9 ± 32
6-min walk					
Mean ± SD (ft)	1135 ± 295	1336 ± 305	1344 ± 304	1264 ± 306	1145 ± 348
% change	NA	23 ± 39	22 ± 35	17 ± 44	14 ± 40
Kaplan-Meier survival	NA	94.3%	93.0%	84.3%	68.6%†

PO, Postoperative; NA, not applicable.

*Mean percentage change of postoperative value from preoperative (after rehabilitation) value.

†P = .53 for Mantel-Haenszel log-rank test comparing Kaplan-Meier survival.

A Cox proportional hazards model assessing for prognostic factors for death was performed (Table 8). This analysis identified advanced age, male gender, low FEV₁, and reduced 6-minute walk distance as statistically significant risk factors for death. A higher risk was also found in patients with a Paco₂ greater than 50 mm Hg and in those with predominantly lower lobe disease. The risk factor for mortality for patients with both a preoperative FEV₁ and a preoperative DLCO no greater than 20% of predicted approached but did not reach statistical significance.

Discussion

LVRs is a palliative treatment for the symptoms of emphysema, designed to relieve dyspnea and improve the ability to

participate in the routine activities of daily living without significant limitation. The operation is to be considered after maximal medical therapy has failed to produce satisfactory palliation. The operation is not intended to retard the naturally progressive course of the underlying disease, but rather is meant to return the emphysematous lung and hyperinflated thorax to an earlier stage in the natural history of obstructive lung disease. Many large longitudinal studies²³⁻²⁶ of patients with severe chronic obstructive pulmonary disease have demonstrated increased mortality relative to the general population. When the FEV₁ is less than 30% of predicted, 50% of patients will die within 3 to 4 years. Two of the major unresolved issues in LVRs are how to select appropriate candidates and how to assess and inter-

TABLE 7. Subgroup analysis comparing pulmonary function and exercise test results before and after surgery between patients with both a preoperative FEV₁ and DLco percent predicted ≤ 20% after rehabilitation and all other patients

	After rehabilitation	6 mo PO	1 y PO	3 y PO	5 y PO
Both FEV ₁ and DLco ≤ 20% (n = 20)					
FEV ₁					
Mean ± SD (L)	0.46 ± 0.1	0.78 ± 0.3	0.81 ± 0.3	0.74 ± 0.3	0.66 ± 0.2
% predicted	17%	32%	31%	25%	24%
% change*	NA	73 ± 63	82 ± 72	47 ± 91	36 ± 52
DLco					
Mean ± SD (mL/ [min · mm Hg])	4.2 ± 0.9	7.0 ± 3.1	7.2 ± 3.2	6.9 ± 3.4	6.2 ± 2.3
% predicted	16%	27%	28%	26%	25%
% change*	NA	70 ± 53	78 ± 62	67 ± 58	51 ± 42
6-min walk					
Mean ± SD (ft)	913 ± 235	1158 ± 289	1179 ± 294	1124 ± 322	1100 ± 204
% change	NA	27 ± 41	28 ± 39	26 ± 42	25 ± 24
Kaplan-Meier survival	NA	95.0%	95.0%	84.4%	59.1%†
All others (n = 230)					
FEV ₁					
Mean ± SD (L)	0.74 ± 0.3	1.12 ± 0.5	1.06 ± 0.5	0.93 ± 0.5	0.82 ± 0.5
% predicted	26%	41%	38%	33%	30%
% change*	NA	52 ± 42	43 ± 44	23 ± 38	6 ± 30
DLco					
Mean ± SD (mL/ [min · mm Hg])	9.3 ± 3.8	10.7 ± 4.6	10.5 ± 4.2	9.4 ± 4.1	8.7 ± 4.3
% predicted	34%	41%	40%	37%	34%
% change*	NA	21 ± 46	16 ± 41	2 ± 31	−8 ± 28
6-min walk					
Mean ± SD (ft)	1161 ± 287	1360 ± 313	1355 ± 308	1284 ± 301	1158 ± 356
% change	NA	23 ± 38	21 ± 35	15 ± 43	2 ± 40
Kaplan-Meier survival	NA	94.8%	93.5%	83.9%	68.9%†

PO, Postoperative; NA, Not applicable.

*Mean percentage change of postoperative value from preoperative (after rehabilitation) value.

†P = .28 for Mantel-Haenszel log-rank test comparing Kaplan-Meier survival.

pret the results. Despite considerable experience, our selection process admittedly contains a significant subjective component, and at our institution we continue to be conservative in our selection criteria. The indications for LVRS have remained essentially unchanged, and we strongly believe that patient selection in terms of both potential benefit and potential risk is key to the success of this procedure. We also strongly believe that rigorous preoperative preparation, including exercise rehabilitation, best prepares these high-risk patients for operation. The morbidity and mortality reported in this group of 250 patients was comparable to that seen in the group of 150 reported on previously. These findings give support to the assertion that we have been consistent and stable in selection and treatment.

The results of the PFTs were characterized by an increase in spirometric parameters and a decrease in lung volumes. Pulmonary rehabilitation increased stamina and exercise tolerance, but it has not been found to produce a change in the FEV₁ or RV between baseline and postrehabilitation values.² The improvement after surgery was statistically significant at each follow-up time point, and FEV₁ and RV were preserved through 5 years in 53% and 80% of patients, respectively. Because medical therapy had been optimized

before the preoperative PFTs, the postoperative improvements in the spirometric parameters must be attributed to the beneficial effects of the surgery and not to the ongoing medical management. The correlation between FEV₁ and life expectancy is well known.²³⁻²⁶ Therefore the improvement in FEV₁ found in all LVRS series may have a substantial impact on patients' longevity, as we demonstrated in a previous report of 87 Medicare patients accepted for LVRS in 1995, 22 of whom were denied the operation because of the subsequent withdrawal of Medicare funding for the procedure.²⁷ At 2 years, objective and subjective measurements of pulmonary function were improved in the surgical group but had worsened in those denied surgery. This report confirmed the natural history of the disease in the patients considered suitable for LVRS, who showed a progressive decline, in contrast to the findings of improved physiologic function seen in patients after the LVRS procedure. Follow-up of these patients to the present reveals a median survival of 3.4 years for those denied the operation versus 5.9 years for those who underwent LVRS.

With regard to the perioperative course, this report echoes previous reports by our group and others that carefully selected patients face a 5% risk of postoperative death. This

TABLE 8. Results of multivariate analysis of prognostic factors influencing survival for patients after bilateral LVRS

Variable	N	Relative risk	95% Confidence interval	P value
Age (y)	250	1.038	1.005-1.073	.026
Gender				
Male	124	Reference	—	—
Female	126	0.543	0.334-0.884	.014
Disease predominance				
Upper lobe	229	Reference	—	—
Lower lobe	21	1.554	0.742-3.254	.242
FEV ₁ (L)*	250	0.213	0.067-0.671	.008
RV (L)*	250	1.013	0.834-1.232	.892
DLCO (mL/ [min · mm Hg])*	250	0.942	0.868-1.022	.154
6-min walk (ft)*	250	0.996	0.994-0.999	.003
FEV ₁ and DLCO†				
All others	230	Reference	—	—
≤20%	20	1.508	0.803-2.835	.094
Paco ₂ (mm Hg)*				
≤50	217	Reference	—	—
>50	33	1.121	0.872-1.631	.126

*Preoperative pulmonary function and gas exchange measurements.

†Both preoperative FEV₁ and DLCO percent predicted measurements up to 20%.

report presents additional long-term follow-up to the mid-term results reported in our last case series report.⁵ The main additions provided by this report are the addition of 100 patients, to add weight to the perioperative statistics of morbidity and mortality, and the addition of substantial follow-up to better describe the natural history of emphysema after bilateral LVRS.

We have consistently stressed the importance of a heterogeneous anatomic distribution of emphysema and made the observation that a low DLCO (<20%) was associated with increased mortality, representing a relative contraindication. The NETT trial recently reported that two groups of patients were found to have high risks for postoperative death and poor functional outcome after LVRS. These two groups were those with a pattern of severe homogeneous emphysematous destruction (homogeneous distribution, FEV₁ ≤20% of predicted) and those with severe functional impairment (FEV₁ and DLCO both ≤20% of the predicted value). These findings corroborate observations from the early LVRS experience, and the statistically sound nature of a prospectively randomized trial has added additional weight of evidence to the belief that such patients are poor candidates. Because we have excluded patients with a homogeneous pattern of emphysematous destruction, our series does not address the issue of whether homogeneous destruction is an absolute or relative contraindication. Others have suggested that highly selected patients with a homogeneous pattern but only moderate functional impairment may receive significant benefit from LVRS.²⁸ Presumably the long awaited results of the NETT trial will shed additional light on this matter.

We also agree that patients with severe functional im-

pairment, as reflected by both FEV₁ and DLCO no greater than 20% of predicted value, have a very high risk. Our series included 20 such patients. Paradoxically, this group of patients achieved a percentage improvement greater than that seen in the rest of the series. The marked improvement in FEV₁ might be expected in this highly selected group of patients with major target areas and low FEV₁. A similar increment in FEV₁ would produce a greater percentage change than observed in patients with higher initial FEV₁. A low DLCO may result either from extensive loss of diffusing surface as a result of emphysematous destruction or from marked hypoventilation of potentially functional pulmonary parenchyma. Such hypoventilation may occur in candidates for LVRS with a heterogeneous pattern of destruction when the marked overinflation of the target areas significantly compromises ventilation to portions of the remaining lung. In this situation, excision of the destroyed areas restores ventilation to better-preserved areas, with a resulting improvement in postoperative DLCO. These patients were selected on the basis of the presumption that the low DLCO was the result of underventilation of preserved lung. The functional improvement after resection of target areas is mirrored by the improved DLCO.

In this series, the major focus of disease was located in the lower lobes in 21 patients, 12 of whom had α_1 -antitrypsin deficiency. These patients have shown significant functional improvement at 6 months after surgery but a decline of benefit at 1 year (Table 6). The explanation for this lack of benefit is not certain. In our early experience, lower lobe resections were smaller than the more extensive resection currently performed. We know from postoperative radiographs and our experience with several of these patients

who subsequently underwent transplantation that the diaphragm was tethered to the chest wall and relatively immobile. Finally, it is possible that these patients had more extensive emphysema than was present in the group with upper lobe predominance. Kaplan-Meier estimation of survival did not show a statistically significant difference between the two groups, although the hazard function in the Cox model suggests that this may have been a sample size issue. Because of this early loss of benefit in lower lobe LVRS recipients, we recommend that only highly selected patients with predominantly lower lobe distribution of disease be considered. This would include patients whose upper lobes show only mild to moderate emphysema on computed tomographic scan and in whom the DLCO is greater than 20% predicted.

Follow-up was essentially complete, avoiding the inevitable bias produced by selective follow-up results. Work by Butler and associates²⁹ suggests that patients lacking follow-up data are the most likely to have a poor result. Previous criticism of the reporting of data from an ever-shrinking cohort of patients followed with time led us to analyze the data from the cohort of patients with complete 5-year follow-up (Table 5). The increase in FEV₁ and decrease in RV occurred primarily during the first year after surgery and, despite the inevitable progression of emphysema, appeared to last at least 5 years. When we looked at the patients who completed the 5-year follow-up with all the measurements at each time point, results therefore did not differ from the results obtained by analyzing all available patients. In this cohort of patients who completed 5-year follow-up, we assessed the rate of decline of half of the benefit. In terms of FEV₁, half of the benefit was lost by 3 years. The most persistent benefit seemed to be in RV, which appeared to be temporally related to sustained reduction in dyspnea and improvement in exercise tolerance. This is not unexpected, because the reduction in residual volume is probably the factor most responsible for the reduced work of breathing, lessened dyspnea, and improved exercise tolerance seen after LVRS. These are all directly a result of thoracic hyperinflation, and a reduction in RV most accurately reflects this reduction. The FEV₁ is a measurement that is easily obtained, highly reproducible, and highly correlated with longevity in patients with severe emphysema.

This report documents a prospective controlled consecutive case series with data acquisition throughout our entire experience with bilateral LVRS. Each patient served as his or her own control, after maximum medical management had been optimized and no further benefit could be achieved. Under these circumstances LVRS was used not as an alternative therapy but as the only potentially efficacious therapy other than, for some, lung transplantation. The natural history of end-stage emphysema is well known and

is documented for patients with end-stage emphysema in general. Furthermore, in six randomized trials comparing LVRS with best medical therapy, LVRS candidates randomly assigned to the medical control arm showed progressive declines in lung function and exercise tolerance. The magnitude of improvement in both objective and subjective outcome measures produced by LVRS was significant, not only statistically but also in terms of impact on the patient's quality of life. Furthermore, the vast majority of patients received a substantial beneficial effect. For all of these reasons—the well documented natural history of progressive decline, the absence of an alternative therapy, the magnitude of the functional improvement, and the frequency of beneficial effects—we chose a prospective controlled consecutive case series rather than a randomized clinical trial to assess the benefit of LVRS. We acknowledge, however, that only a randomized clinical trial can provide a true estimate of the “value” of the procedure by comparing the benefit achieved with the operation with the progressive decline exhibited by an identical control group. Furthermore, only a long-term randomized clinical trial in which half of the patients are denied access to the operation can accurately define the effect of LVRS on longevity.

Conclusion

Our experience leads us to conclude that careful patient selection, rigorous preoperative preparation, and detailed operative and perioperative care are all necessary for successful LVRS. The operation appears to provide improved pulmonary function and quality of life, increased exercise tolerance, and decreased requirement for supplemental oxygen. The most recent follow-up data confirm persistent objective benefits at 5 years for most patients.

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Discussion

Dr Larry R. Kaiser (Philadelphia, Pa). Let me state at the outset that the only conflict I have is that I have been a tremendous

admirer of Dr Cooper ever since I was his resident about 18 years ago, if that counts as a conflict. I appreciate the opportunity to discuss this important article. My congratulations to Dr Ciccone, the current Graham Memorial Traveling Fellow, for an outstanding presentation. This is an important article for a number of reasons. It is the first report detailing long-term follow-up for patients undergoing LVRS. With a median follow-up of 4.4 years, we now know the natural history of the disease progression after the surgical procedure. Remarkably, only 1 patient was unavailable for follow-up. The study was carried out as a prospective controlled consecutive case series, with data collected from the beginning of the experience. Ciccone and colleagues have demonstrated that, with careful patient selection, the operation can be accomplished with less than 5% perioperative mortality, with most patients showing a significant improvement in quality of life, and they have shown how long this improvement lasts. They have delineated the selection factors that define the optimal patient for this operation and have convincingly demonstrated that for these selected patients LVRS is a superior alternative to the best medical therapy.

Should we discount the results presented today because the study design was not experimental; that is, it did not involve random assignment of treatment? I would argue, and this view is supported by others who have looked at the question in considerably greater detail than I, that a carefully designed observational study such as this can provide results equivalent to those that can be obtained by a randomized trial. Short of demonstrating a survival advantage for the procedure, a claim never made by those doing the operation, a randomized trial would add little. Six randomized trials have already demonstrated a significant treatment advantage in the group undergoing operation. This study extends the information from the randomized trials in that it answers questions regarding long-term results.

I have several questions, Dr Ciccone. First, in the article you discussed a change in the operative technique from an oblique line of parenchymal resection to a transverse one, removing almost the entire upper lobe. What led to this change, and do you think that this influenced the outcomes of the more recent patients? Have you been able to define guidelines regarding how much lung to resect? Patients with basilar disease had an early improvement in function similar to that in those with apical disease but showed a rapid decline. Would you still operate on patients with basilar disease? Finally, 9 patients had non-small cell lung cancer found in the resected specimen, and in 4 of these the finding was purely incidental. Have any of these 9 patients died of lung cancer? Did any patient have an incomplete resection that, under ideal circumstances, would have prompted a reoperation?

I end by noting that the information needed by the Centers for Medicare and Medicaid Services for a coverage decision has just been presented. I can only hope that the powers that be at the Centers for Medicare and Medicaid Services get the message so that selected Medicare patients with emphysema can benefit from this procedure.

To repeat, my first question concerned the change in the technique from the oblique resection to the transverse resection. Did that make any difference in the results in the later patients?

Dr Ciccone. Regarding the shift to a transverse resection, we do not think that this has made a lot of difference. I have several times heard Dr Cooper say the day after surgery that he wished he

had cut out less lung, because of a pleural space problem. Six months after surgery, however, he wished he had cut out more parenchyma, because the good results probably would have been even better.

Dr Kaiser. Do you have any guidelines as to how much to resect?

Dr Ciccone. No, there are no precise guidelines. The technique changed from an inverted U-shape that goes from the anterior aspect of the upper lobe toward the apex and then down the back. The current technique is just a resection from the front, straight toward the back, removing almost all of the upper lobe on the right. On the left, the portion of the upper lobe is removed almost completely, and just the lingula is left intact.

Dr Kaiser. My third question concerned those patients with basilar disease—lower lobe disease. They showed an early improvement that did not seem to last. Do you still operate on such patients?

Dr Ciccone. We still operate on these patients. We had 21 of these patients in this series, and 12 of these had a deficiency of the enzyme α_1 -antitrypsin. We just recommend that surgeons be highly selective with such patients. Although they showed good results at 6 months, exactly the same as the other patients with the upper lobe predominance of disease, they appeared to lose the benefit of this operation more rapidly.

Dr Kaiser. Nine patients had lung cancers. Have any of those patients died of their malignancies? And in 4 cases the disease was found by the pathologist and not noted at the time of operation. Were any of those incomplete resections?

Dr Ciccone. Of these 9 patients, 5 were known to have malignancy before the operation. In the other 4 cases, it was found at surgery. As for late death after LVRS, 84 of these patients died, and 4 of the 9 patients with carcinoma died late after the operation, 2 of the 4 of recurrent carcinoma and the remaining 2 of respiratory failure. I do not have available other specific details on the deaths of the 9 patients with cancer in the resected specimen.

Dr Thomas W. Rice (Cleveland, Ohio). I compliment this group for leading the charge in showing that we can get good results with careful follow-up of our patients. Dr Ciccone, can you tell us how you are going to apply this information to your patients in Rome? How will you use this study to help you select patients in Rome for LVRS?

Dr Ciccone. We already do this kind of operation in Rome. Our group of patients is not so consistent, and we alternate on a case-by-case basis between median sternotomy, which is our first

choice, and thoracoscopy, which we use for severely compromised patients. In Rome, as in this series, the unilateral procedure is given to selected patients, typically patients with contraindications to bilateral LVRS.

Dr Rice. Can you tell us any operative hints that Dr Cooper has taught you?

Dr Ciccone. Well, I don't know whether I am allowed to say that. Probably Dr Cooper should answer this question.

Dr Joseph E. Bavaria (Philadelphia, Pa). I just wanted to ask you two questions. First, what was the percentage of patients who ended up with single-lung transplants?

Dr Ciccone. I don't remember the exact percentage, but there were 18 patients who underwent transplantation after LVRS.

Dr Bavaria. Second, what was their mean age?

Dr Ciccone. The mean age of the patients undergoing LVRS was 62 years.

Dr Bavaria. And those undergoing transplantation?

Dr Ciccone: The mean age of patients who underwent LVRS and went on to lung transplantation was 54 years.

Dr Cooper (St Louis, Mo). Thank you for the opportunity, and thank you, Anna Maria, for a wonderful presentation. I have a lot of people to thank, my colleagues and the people at our institution, who in spite of the political maelstrom associated with this operation have been extremely supportive, and I am grateful to them.

This operation has become a lightning rod, because it occurred in a day when evidence-based medicine is being used as the watchword as to how new procedures should be introduced. I think that we have all learned something. There is no question that after the initial presentation at this meeting in, I believe, 1994, a lot of people began doing some sort of LVRS, often with poor selection and inadequate resources, and this led to a lot of problems. I think it behooves us all to look carefully at how we can introduce new procedures and new technologies in a responsible fashion and avoid hype, avoid exaggerated claims, and do it in an objective manner. It is important for our patients, for payers, and for society to ensure that new procedures are introduced in a careful and cautious yet timely fashion. I am not sure that we have a mechanism yet in this country for such a process, but I think that organizations such as this can play a major role.

I don't know any tricks yet. This is not a technically difficult operation. It is deceptively simple, and perhaps therein lies the danger. The trick is really in the selection and the postoperative care of the patients, and my colleagues and our staff have a lot more to do with that than I do.