Lung Volume Reduction Surgery vs Medical Treatment*

For Patients With Advanced Emphysema

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Objective: **To contribute to the knowledge on the therapeutic value of lung volume reduction surgery (LVRS).**
Design: **Two similar, independently conceived and conducted, multicenter, randomized clinical trials.**
Setting: **The Canadian Lung Volume Reduction (CLVR) study and the Overholt-Blue Cross Emphysema Surgery Trial (OBEST).**
Methods: **Using a fixed-effects meta-analysis, the 6-month results produced by the addition of LVRS to optimal medical therapy were compared to those obtained from optimal medical therapy alone. Patients were required to have severe emphysema, marked airflow limitation (*ie*, FEV_1, 15 to 40% predicted), hyperinflation (total lung capacity [TLC], > 120% predicted), CO_2, < 55 mm Hg, and measurable dyspnea (chronic respiratory disease questionnaire [CRDQ] scores ≤ 4 for the CLVR study, or Medical Research Council dyspnea scale ≥ 1 for the OBEST). Optimal medical therapy included pulmonary rehabilitation in both arms of both studies.**
Results: **The CLVR study randomized 58 patients and the OBEST randomized 35 patients for a total of 93 patients. Of these, 54 patients were randomized to undergo surgery, and 39 patients were randomized to receive medical treatment. The 6-month mortality rate (including operative mortality) in the surgical and medical cohorts was similar (5.6% vs 5.1%, respectively). A comparison of the medical and surgical arms of the combined CLVR study/OBEST population showed that LVRS was associated with a higher FEV_1 (167 mL or 24% predicted; 95% confidence interval [CI], 29 to 304; p = 0.017), lower residual volume (−1,342 mL or 24.5% predicted; 95% CI, −1,844 to −840; p < 0.001), lower TLC (−1,044 mL or 13% predicted; 95% CI, −1483 to −605; p < 0.001), and higher 6-min walk distance (148.8 feet; 95% CI, 24.3 to 273.2; p = 0.019). Each domain of the CRDQ showed statistically significant improvement in the surgical arm of the study, but not in the medical arm. The summary physical component scale of the Medical Outcomes Study 36-item short form (SF-36) was also more favorable in the LVRS cohort (6.9; 95% CI, 2.86 to 10.90; p < 0.001). The summary mental component scale of the SF-36 did not show a statistically significant difference between the two groups.**
Conclusion: **Six months after randomization, LVRS produced better palliation than optimal medical therapy in patients with advanced emphysema.** ***(CHEST 2005; 127:1166–1177)***

Key words: chronic obstructive lung disease; COPD; emphysema; lung volume reduction; pneumectomy; quality of life; randomized multicentered clinical trial; surgery

Abbreviations: CI = confidence interval; CLVR = Canadian Lung Volume Reduction; CRDQ = Chronic Respiratory Disease Questionnaire; DCC = data coordination center; DLCO = diffusing capacity of the lung for carbon monoxide; HUI = health utility index; LVRS = lung volume reduction surgery; 6MWD = 6-min walk distance; NETT = National Emphysema Treatment Trial; OBEST = Overholt-Blue Cross Blue Shield Emphysema Surgery Trial; RV = residual volume; SF-36 Medical Outcomes Study 36-item short form; TLC = total lung capacity

The report by Cooper et al[1] in 1995 on the beneficial influence of lung volume reduction surgery (LVRS) for the treatment of advanced emphysema was followed by enthusiastic utilization of the operation. During the early experience with LVRS, functional results, and operative mortality as well as morbidity had been highly variable.[2] However, as the indications for the procedure and principles of management evolved and became standardized, the results were favorable and relatively

uniform. The scores of observational studies indicated that 70 to 80% of selected patients experienced clinical and physiologic improvements with acceptable operative mortality rates (range, 4 to 8%).

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Nonetheless, skepticism about the effectiveness of the operation was widespread.[3] Concern was also expressed[4] that, in the face of as many as 1 million potential candidates for LVRS in the United States alone and a cost of $30,000 to $35,000 per operation, unfettered utilization would impose a heavy burden on the health-care budget. Health insurers, including Medicare, discontinued the coverage of LVRS, and utilization of the operation fell sharply. Many patients and physicians were disappointed by the denial of access to a seemingly effective therapeutic modality for a devastating chronic disease. In response, several, single-center, randomized clinical trials and the National Emphysema Treatment Trial (NETT), sponsored by the National Institutes of Health and Medicare, were organized to assess the effectiveness of the operation, to clarify the indications, to refine the details of management, to determine the duration of benefits, and to obtain information about the impact on longevity.[3,5–11] Unfortunately, all the randomized LVRS trials were hindered by poor enrollment. Although favorable results were reported from five smaller randomized trials,[5–9] none of them enrolled sufficiently large numbers to draw convincing conclusions about the value of LVRS. A May 2003 report from the NETT[11] provided valuable outcome information on 1,218 patients, but the search for definitive answers about the value of LVRS is continuing.

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The Canadian Lung Volume Reduction (CLVR) surgery study and the Overholt-Blue Cross Emphysema Surgery Trial (OBEST) are two independent multicenter randomized clinical trials with study designs, patient characteristics, clinical care, databases, and outcomes that are sufficiently similar to permit a meta-analysis of the combined results. Since both trials experienced enrollments that were lower than expected, it was thought that combining the data from the two studies[3,10] provides greater statistical power to answer questions about the palliative value of LVRS. The present study reports on the combined 6-month outcomes from these two multicenter clinical trials.

Materials and Methods

The Randomized Clinical Trials

The CLVR study was a Canada-wide, four-center, randomized clinical trial comparing treatment with LVRS combined with optimal medical therapy and optimal medical therapy alone for patients with advanced emphysema. The optimal medical therapy included the completion of a 6-week regimen of standardized pulmonary rehabilitation. The primary outcome of this trial is the health utility index (HUI), a measure of health-related quality of life, over the 2-year follow-up period. Because the CLVR study continued to enroll new subjects, we chose not to evaluate the primary outcome for this interim assessment. Enrollment was conditional on specified inclusion and exclusion criteria (Tables 1, 2). After a standardized screening and evaluation process, patients who qualified were randomized in a 1:1 allocation ratio to receive treatment with LVRS plus optimal medical therapy or optimal medical therapy alone, with surgeon stratification and blocking within each center. Blocking was performed in groups of two or four. Patients who were assigned to undergo LVRS proceeded to surgery within 2 weeks. Crossover between randomized arms was not permitted (Fig 1). No patient crossed over from medical therapy to LVRS during the first 6 months of randomized treatment. Patient recruitment started in July 1997 and finished in September 2001.

The OBEST was also a randomized clinical trial[3] that compared outcomes from LVRS combined with optimal medical therapy and optimal medical therapy alone for patients with advanced emphysema. Optimal medical treatment included 80% compliance with a standardized 8-week pulmonary rehabilitation program. The primary objective of this trial was to detect differences in outcome between the two arms in terms of health-related quality of life, as measured by the chronic respiratory disease questionnaire (CRDQ), and exercise capacity, as measured by the 6-min walk distance (6MWD). Eligibility was determined by specified inclusion and exclusion criteria that were similar to those in the CLVR study (Tables 1, 2). All 11 participating hospitals, which were located in the Commonwealth of Massachusetts, screened and managed patients, while LVRS was performed in only six hospitals. As Blue Cross Blue Shield of Massachusetts and Harvard Pilgrim Health Care agreed to cover the costs of clinical care, the overwhelming majority of patients were subscribers to these two health plans. Patients were randomized for 6 months of treatment in a 2:1 allocation ratio between surgery and medicine within blocks of six patients, and this was done for each referring center. The 6-month randomization period with a crossover option from medicine to surgery

Table 1—*Inclusion Criteria

Criteria	CLVR Study	OBEST
Clinical diagnosis	Advanced emphysema	Advanced emphysema
Severity of dyspnea	CRQ ≤ 4	MRC ≥ 1
Age	≤ 80 yr	≤ 75 yr
FEV_1, % predicted	15–40%	< 40%
FEV_1 response to bronchodilator		
% predicted	< 30	< 30
mL	< 300	< 300
TLC, % predicted	≥ 120%	> 125%
RV, % predicted		> 175%
RV/TLC ratio of % predicted	≥ 60%	
P_{CO_2}, mm Hg	< 55	< 55
CT scan evidence of emphysema	Yes	Yes
Heterogeneous upper lobe emphysema by CT scan	No	Yes
Compliance with rehabilitation	Yes	Yes
BMI/ideal body weight	17–32 kg/m^2	75–125%
6MWD, feet		≥ 492

*BMI = body mass index.

after the completion of the 6-month evaluation was elected because by that time the results of the operation were manifest and reliable outcome data were available. Moreover, delaying a potentially beneficial therapeutic intervention (*ie*, LVRS) for this relatively short period does not expose the patient to undue health hazards, as emphysema progresses relatively slowly and is not usually associated with sudden death (Fig 1). The recruitment of patients started in October 1998 and finished in January 2002.

The clinical trial protocols and other relevant documents were reviewed and approved by the ethics committee or institutional review board for each participating institution. Patients in the study signed appropriate informed consent forms. Each trial had its own data safety monitoring board. As the CLVR study and the OBEST used essentially identical protocols for patient selection, treatment, and data collection, the studies were suitable for meta-analysis.

Center Selection

Site selection for both the CLVR study and the OBEST was based on documented LVRS experience with an acceptable operative mortality rate (< 10%), morbidity, and functional results. Other criteria for site selection included the availability of experienced pulmonologists and thoracic surgeons in institutions with up-to-date operating and intensive care facilities, which were staffed by multidisciplinary support teams that included critical care, anesthesia, and thoracic radiology specialists.

Table 2—*Exclusion Criteria*

Criteria	CLVR Study	OBEST
Receiving mechanical ventilation	Yes	Yes
α_1-antitrypsin deficiency	Yes	Yes
Bullous disease > 5 cm	Yes	Yes
Chest wall deformity	Yes	Yes
Bronchiectasis with excessive sputum	Yes	> 3 tablespoons/d
Prior thoracotomy	Yes	Yes
Obliterated pleural space	Yes	Yes
Pulmonary nodule	Yes	≥ 0.7 cm
Prednisone qd, mg	> 10	> 15
Pulmonary hypertension, mm Hg	≥ 30	≥ 35
Severe comorbidities*	Yes	Yes
Life expectancy, yr	< 1	< 2
Registered for lung transplant	Yes	Yes

*Comorbidities include hypertension, diabetes, previous cerebral vascular accident, and renal disease.

Patient Selection and Screening Process

Patients who had received a clinical diagnosis of emphysema and had severe shortness of breath, despite receiving optimal

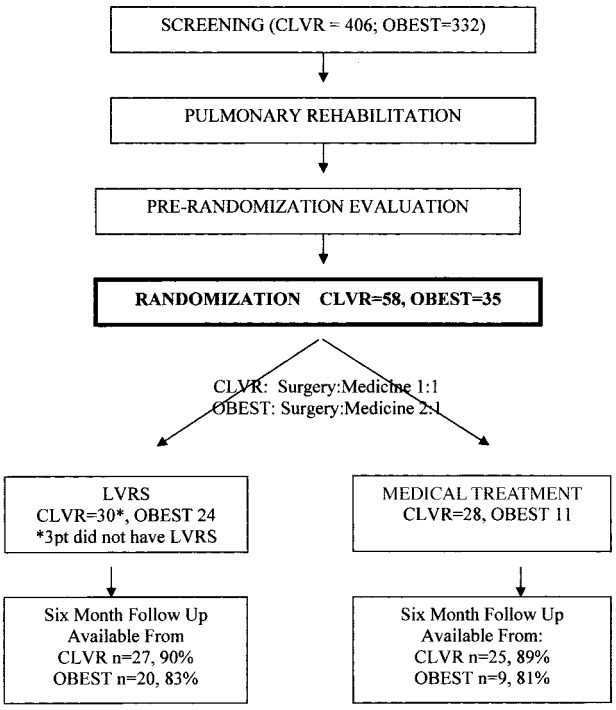

FIGURE 1. Flow diagram for the CLVR study and the OBEST outlines the progress from initial screening, through assessment for eligibility, to the 6-month follow-up visit. pt = patients.

medical therapy, were accepted for screening by both the CLVR study and the OBEST. Although the inclusion and exclusion criteria were established independently by the CLVR study and the OBEST, both studies followed commonly practiced standards at the time the respective studies were organized, and thus the selection criteria for the two trials were similar (Tables 1, 2). During the first clinic visit, written informed consent for initial screening and testing was obtained. A medical history was obtained, and a physical examination was performed. Patients who qualified for further evaluation were referred for a battery of laboratory tests that included, but were not limited to, spirometry, lung volume determination by plethysmography, diffusing capacity of the lung for carbon monoxide (DLCO), chest radiographs, standard and high-resolution CT scans, ventilation/perfusion scans, transthoracic echocardiogram to assess cardiac variables and pulmonary artery pressure, ECG, arterial blood gas levels, CBC count, and liver and kidney function tests. All patients were tested for α_1-antitrypsin deficiency. In both trials, a single 6MWD test was performed, during each clinic visit, by a professional trained in a standardized method. Health-related quality-of-life was assessed by the disease specific CRDQ and by the generic Medical Outcomes Study 36-item short form (SF-36).[12,13]

Standardization of Programs and Outcome Measure Testing

Pulmonary rehabilitation programs, and the assessment of health-related quality of life and outcome measures such as the 6MWD were standardized in all centers with the use of training sessions, training videos, annual refresher meetings for investigators, a study-specific manual of treatment guidelines, and trial co-coordinator meetings. Pulmonary function testing facilities participating in both trials met or exceeded the standards established by the American Thoracic Society. The reference values used to estimate the percentage of predicted FEV_1, residual volume (RV), and total lung capacity (TLC) also complied with American Thoracic Society recommendations.[14] Every effort was made to blind those persons who were administering outcome measure tests to the allocation group of the study participants. However, as in all surgical clinical trials, blinding was difficult to ensure in all instances.

Radiologic Testing

In both the CLVR study and the OBEST, the CT scans of the chest were interpreted locally at the various participating institutions to determine patient eligibility for enrollment into the trials. The CT scan images then were transferred to an imaging center for further study. The radiologic criteria for entry into both the CLVR study and the OBEST required evidence of hyperinflation with flattened diaphragms and an increased anteroposterior diameter, which are indicative of advanced emphysema. CT scan evidence of emphysema severity was subjectively assessed, as was the degree of heterogeneity. An absence of dominant lower lobe emphysema was required for patients in the OBEST study. Patients who had severe saccular bronchiectasis (*ie*, production of more than three tablespoons of sputum per day) or giant bullous emphysema (defined as one or several bullae > 5 cm in size or occupying $> 25\%$ of the volume of the hemithorax compressing the surrounding lung parenchyma) were excluded. Patients with pulmonary nodules that were > 0.7 cm in size, that had been present for < 2 years, that showed increases in size, or that had malignant features were also excluded from the study. In the end, the patients' prospective surgeon made the final decision about their suitability for participating in the study.

Randomization

During a second clinic visit, the results of the laboratory tests were reviewed, and the patients were reevaluated. Those who qualified for the trial signed a second informed consent form, and were referred for participation in a standardized pulmonary rehabilitation program that was of a similar nature and duration in the two trials. After completing pulmonary rehabilitation, a second round of prerandomization testing was performed and used as the baseline values. Patients who were still eligible for the trial were randomized between LVRS combined with optimal medical therapy and optimal medical therapy alone. The randomization was performed by the data coordinating center for each study. All outcome events were attributed on an intent-to-treat basis. Patients who were randomized to undergo surgery were scheduled to undergo LVRS within 14 days, but not exceeding 21 days, after randomization. The study design is presented schematically in Figure 1.

Outcome Objectives

The primary outcome objective for the CLVR study was HUI, and for the OBEST the objectives were the CRDQ score and the 6MWD. A predetermined minimally clinically important difference for the 6MWD was considered to be 30 m (100 feet). The secondary objectives for both trials included the SF-36 and changes in pulmonary physiology (*ie*, FEV_1, TLC, and RV). We aimed to reduce the RV by 20 to 30% and considered the minimally clinically important difference for FEV_1 to be 200 mL or an increase from baseline of 20%. The CLVR study also used the 6MWD as a secondary objective. All these variables, except for the HUI, were obtained and analyzed in the present meta-analysis.

CRDQ

The CRDQ is an interviewer-administered instrument measuring both physical and emotional aspects of chronic respiratory disease.[12] The instrument contains a total of 20 questions in four categories (*ie*, dyspnea, fatigue, emotional function, and mastery). Each item is scored on a 7-point modified Likert scale from 1 (maximum impairment) to 7 (no impairment). Changes in the score of 0.5, 1.0, and 1.5, respectively, were regarded as small, moderate, and large effects.

SF-36

The SF-36 is a self-administered questionnaire and contains 36 questions covering eight health domains divided into two components.[13] The physical component summary scale scores includes physical functioning, role physical, bodily pain, and general health perceptions, while the mental component summary consists of energy/vitality, social functioning, role emotional, and mental health. Each domain is scored from 0 to 100, with the highest number representing the best health state. In this study, 5 was considered to be a small change in score, while 10 was considered to be a moderate-to-large change in score.

Surgical Technique

Surgical techniques were standardized independently in the CLVR study and the OBEST, but on retrospective analysis they were similar in both trials. The CLVR study used median sternotomy in all patients, as did five of the six OBEST centers. One OBEST site employed video-assisted thoracic surgery exclusively (six patients). The most severely diseased portions of the

upper lobes of both lungs were identified by preoperative CT scans of the chest and by ventilation perfusion scans. This preoperative information was combined with the anatomic findings at surgery for the determination of the site and extent of resection. Approximately 20 to 30% of the total lung volume was removed with linear staplers. The staple lines were buttressed with either bovine pericardium or polytetrafluoroethylene (Gore-Tex; W. L. Gore; Sunnyvale, CA) to reduce postoperative air leaks.[15,16] Extubation was attempted in the operating room immediately after consciousness returned in all patients.

Medical Treatment

Medical treatment for patients in both the CLVR study and the OBEST was optimized according to the recommendations of the American Thoracic Society and the Canadian Thoracic Society. Medical therapy included pulmonary rehabilitation, smoking cessation, yearly vaccination, oxygen therapy, and therapy with bronchodilators, corticosteroids, and antibiotics.[17–20] Patients in both arms of the study completed a standardized pulmonary rehabilitation program of at least 6 weeks duration prior to randomization and continued with the program for the full duration of the study.

Patient Follow-up and Disposition

Intensive efforts were made by both trials to follow up patients for the duration of the study. Data for the 6-month follow-up were collected any time between 24 and 28 weeks after randomization (mean [± SD] time, 6 months ± 2 weeks). After the 6-month evaluation mark, patients in the medical arm of the OBEST who expressed a desire to undergo LVRS and still qualified for the procedure were given the opportunity to undergo surgery.

Sample Size

The sample size in the CLVR study was calculated assuming a two-tailed type I error rate (α) of 5%, a power of 90%, and a clinically important difference (Δ) of 0.10 over the 2-year period of follow-up in the trial for HUI. Therefore, a total sample size of 350 patients, with a 1:1 allocation ratio and blocking within centers, was calculated. Similarly, in OBEST, the sample size was calculated using a two-sided test at the 5% significance level with a 90% power to detect a 100-foot difference in the 6MWD between the two arms. Expecting a withdrawal rate of approximately 15% by the time of the 6-month evaluation, a total sample size of 219 patients with a 2:1 allocation ratio was calculated.

Data Management and Analysis

The CLVR study and the OBEST contracted with separate data coordination centers (DCCs) for randomizing patients and managing data. All of the data collected were entered into case report forms at the participating clinical sites and were submitted to the respective DCCs for analysis. The combined data from the two studies were analyzed by the DCC of the CLVR study. Although we chose to present the two studies in a meta-analysis format, this report does not include data from all other available studies. We thought, however, that the meta-analysis approach was both acceptable and the fairest way to present the results of these two independent studies together. Study designs, patient groups, and clinical management were similar for the CLVR study and the OBEST, allowing for a combined assessment of the two trials. A statistical test of heterogeneity was performed between these two trials and produced a test statistic (Q), which when compared to a χ^2 distribution gave p values of 0.19, 0.34, 0.56, and 0.73, respectively, for the SF-36 mental component, the SF-36 physical component, FEV_1, and 6MWD. These results suggest that the two trials were not different, that one should not reject the null hypothesis, and that the difference in the true treatment effects could be reported in this manner. Thus, both clinical and statistical criteria showed sufficient similarity to allow the analysis of the combined data.

Data are presented as the mean and SD. Differences between groups (surgical cohort and medical cohort) at 6 months are presented and evaluated. Similarly, the differences between baseline (postrehabilitation and prerandomization) and the 6-month postrandomization values (changes within a cohort) are also presented. The primary tool for the assessment of data was a two-way analysis of variance with center and treatment as the two factors. The primary and secondary analyses were conducted at the 5% level of significance. The results from each of the studies and from combining the two studies were evaluated. Pooling was conducted using 6-month results for the meta-analyses. The meta-analysis was modeled along the method suggested by Sutton et al.[21] Pooled results were expressed as the weighted mean differences with 95% confidence interval (CI) using the fixed-effects model, in which weights were chosen as inverse variances of the treatment effect.

Findings

The CLVR study screened 406 patients. Of these, 348 patients (85.7%) did not meet the inclusion/exclusion criteria and were disqualified, leaving 58 patients for randomization (Fig 1). Reasons for exclusion were pulmonary function test results outside the acceptable boundaries (34%), prohibitive comorbidity (25%), bullous disease (9%), patient refusal to participate (17%), α_1-antitrypsin deficiency (6%), patient preference for lung transplantation (5%), and ventilator dependency (4%) [Fig 1].

The OBEST screened 332 patients. Of these, 221 patients were disqualified after the initial evaluation because of a failure to meet the inclusion/exclusion criteria or because they did not have the required insurance coverage. Of the 111 patients who qualified for further screening, 76 patients either failed to meet the inclusion/exclusion criteria or refused randomization. The remaining 35 patients completed pulmonary rehabilitation and were randomized (Fig 1).

The CLVR study randomized 58 patients, and the OBEST randomized 35 patients, for a total enrollment of 93 individuals in the two trials. Thirty patients from the CLVR study and 24 patients from the OBEST were randomized to undergo LVRS, for a total of 54 planned operations. In the CLVR study trial, three patients did not undergo LVRS. One of these patients withdrew from the study prior to undergoing LVRS and refused to be followed up further. A second patient's operation was postponed and, on reassessment 4 months later, he felt too well to accept the risks of surgery. All scheduled outcome measures were obtained, and this patient was in-

cluded in the surgical cohort results (intent to treat). A third patient was disqualified in error from the study because of an unexpected intraoperative discovery of a lung malignancy.

The medical cohort consisted of 28 patients from the CLVR study and 11 patients from the OBEST, for a total of 39 patients. Because of the 2:1 surgical/medical randomization in the OBEST design, the medical arm in the OBEST was smaller than the surgical cohort. From the original 93 randomized patients, 5 patients died during the follow-up period and only 88 patients survived to undergo evaluation 6 months after randomization. Pulmonary function test results were obtained in 79.5% of patients (70 of 88 patients), CRDQ scores were obtained in 85.2% of patients (75 of 88 patients), SF-36 scores were obtained in 85.2% of patients (75 of 88 patients), and 6MWD results were obtained in 90.9% of patients (80 of 88 patients).

The inclusion/exclusion criteria were essentially the same in the two studies. One exception was that the OBEST accepted patients with a heterogeneous distribution of emphysema, while the CLVR study also included two patients with homogeneous disease. Thus, 91 of the 93 randomized patients (97.8%) had predominantly heterogeneous upper lobe disease. The two patients with homogeneous anatomy in the CLVR study had FEV_1 values of $> 20\%$ predicted and thus did not meet the "high-risk criteria" of the NETT (Tables 1, 2).

The demographic profiles and the baseline data in the surgical and medical arms of the two trials were similar (Table 3). The surgical arm of the OBEST had more women than men. Every patient studied in the two trials exhibited the hallmarks of advanced emphysema.

Of the 54 patients who were randomized to undergo LVRS, only 51 underwent the procedure. There was one hospital death (1 of 54 patients [1.85%] or 1 of 51 patients [1.96%]). An additional two surgical patients (3.8%) died > 30 days after undergoing LVRS but within 6 months after undergoing LVRS, for a total 6-month mortality rate of 5.7% in the operative cohort. One of the late deaths occurred 4 months after surgery. The other patient died 6 months after undergoing LVRS from an apparent unrelated cardiac event. In the medical arms of the CLVR study and the OBEST, two of 39 patients (5.1%) died within 6 months of randomization.

The median length of hospital stay for LVRS was 22 days (range, 4 to 161 days) in the CLVR study and 12 days (range, 4 to 57) in the OBEST. During the 6-month follow-up period, the CLVR study hospitalized 14 medical patients (50%) for 38 hospitalizations and 18 post-LVRS patients (60%) for 27 readmissions. During the same time frame, the OBEST hospitalized one medical patent (9%) on one occasion and three post-LVRS patients (12.5%), for a total of three hospitalizations.

Changes From Baseline to 6-Month Postrandomization Values

Pulmonary Function: Spirometry and lung volume measurements showed improvement between baseline and 6-month postrandomization values in the surgical arms of the CLVR study, the OBEST, and the combined population (Table 4). In the LVRS cohort of the combined CLVR study/OBEST population, FEV_1 increased by 192 mL (28.8%), the TLC and RV decreased by 993 mL (12.4%) and 1351 mL (24.3%), respectively, P_{CO_2} fell by 2.9 mm Hg, and DLCO rose by 1.11 mm/min/mm Hg. All of these changes were statistically significant. In the medical arms of the CLVR study, the OBEST, and the combined population, the pulmonary function test, DLCO, and P_{CO_2} values showed slight changes that were not statistically significant. FEV_1 fell by 10.2%, but this did not reach statistical significance (Table 4).

Exercise Tolerance: The 6MWD increased in the surgical cohorts and decreased in the medical arms of both the CLVR study and the OBEST. In the combined population, the 6MWD increase in the surgical group was 145.5 feet ($p = 0.032$), and the 6MWD decrease in the medical arm was 57.9 feet ($p = 0.085$) [Table 4].

Outcome Differences Between Surgical and Medical Arms 6 Months After Randomization

Pulmonary Function: Six months after randomization, FEV_1, TLC, RV, and P_{CO_2} showed better values in the surgical arms than in the medical arms of the CLVR study, the OBEST, and the combined population. In the latter, all of the differences, except for DLCO, were statistically significant (Table 5).

Exercise Tolerance: The 6MWD was greater in the surgical than in the medical cohorts of both the CLVR study and the OBEST In the combined population, the 6MWD advantage by the LVRS cohort was statistically significant (Table 5).

An assessment of the overall 6MWD results revealed that months after randomization a much higher percentage of the LVRS patients had improved than had deteriorated in both the CLVR study and the OBEST. The medical cohort exhibited a reverse ratio. In the combined LVRS population, the performance of 62% of the patients improved,

Table 3—*Baseline Demographics*

Baseline	CLVR Study			OBEST			Combined		
	Surgery (n = 30)	Medical (n = 28)	Total (n = 58)	Surgery (n = 24)	Medical (n = 11)	Total (n = 35)	Surgery (n = 54)	Medical (n = 39)	Total (n = 93)
Age,* yr	64.32 (7.30)	63.35 (7.38)	63.85 (7.29)	63.02 (5.25)	65.74 (5.98)	63.87 (5.55)	63.75 (6.44)	64.02 (7.02)	63.86 (6.65)
Gender									
Male	21	18	39	9	7	16	30	25	55
Female	9	10	19	15	4	19	24	14	38
BMI,* kg/m^2	24.15 (4.63)	23.35 (3.46)	23.76 (4.09)	23.01 (3.80)	25.60 (2.84)	23.83 (3.69)	23.64 (4.27)	24.00 (3.41)	23.79 (3.92)
Smoking,* pack-yr	57.39 (19.93)	44.73 (14.23)	51.06 (18.30)	72.38 (37.40)	70.55 (29.33)	71.80 (34.64)	64.58 (30.27)	52.41 (22.86)	59.40 (27.89)
Comorbidities,†‡ No.	7 (23)	3 (11)	10 (17)	3 (13)	3 (27)	6 (17)	10 (19)	6 (15)	16 (17)
CRDQ dyspnea*	3.42 (0.98)	3.37 (0.79)	3.39 (0.88)	3.58 (1.50)	3.66 (1.10)	3.61 (1.37)	3.50 (1.25)	3.45 (0.89)	3.48 (1.10)
FEV_1,‡ mL	715 (23.8)	646 (22.8)	682 (23.3)	665 (22.9)	779 (26.5)	701 (24.0)	693 (23.4)	683 (23.9)	689 (23.6)
RV,‡ mL	5,469 (247)	5,388 (257)	5,429 (252)	5,678 (280)	4,900 (221)	5,433 (261)	5,563 (262)	5,250 (247)	5,431 (255)
D_{LCO},* mL/min/mm Hg	8.23 (3.70)	8.71 (3.40)	8.47 (3.54)	6.71 (2.34)	8.42 (2.57)	7.25 (2.51)	7.58 (3.24)	8.63 (3.15)	8.00 (3.23)
TLC,* L	8.23 (1.53)	7.80 (1.42)	8.02 (1.48)	7.79 (1.76)	7.29 (0.89)	7.64 (1.55)	8.03 (1.64)	7.66 (1.30)	7.87 (1.51)
P_{CO_2},* mm Hg	45.93 (7.05)	45.46 (8.66)	45.70 (7.81)	43.88 (7.47)	42.46 (6.20)	43.43 (7.04)	45.00 (7.24)	44.62 (8.08)	44.84 (7.57)
P_{O_2},* mm Hg	67.38 (12.49)	65.93 (18.41)	66.67 (15.56)	69.42 (11.22)	68.18 (8.62)	69.03 (10.36)	68.30 (11.86)	66.56 (16.17)	67.57 (13.80)
6MWD,* feet	1,125 (361)	1,051 (285)	1,090 (325)	1,017 (300)	1,231 (312)	1,084 (316)	1,077 (337)	1,102 (299)	1,087 (320)
SF-36 utility*	0.648 (0.110)	0.622 (0.128)	0.635 (0.119)	0.687 (0.121)	0.673 (0.078)	0.683 (0.108)	0.665 (0.115)	0.636 (0.118)	0.654 (0.117)

*Values in parentheses are SD.

†Comorbidities include hypertension, diabetes, previous cerebrovascular accident, and renal disease.

‡Values in parentheses are %.

Table 4—*Changes in Outcome Values From Baseline to 6 Months Postrandomization*

Test	CLVR Study		OBEST		Combined Population	
	Surgical	Medical	Surgical	Medical	Surgical	Medical
FEV_1,* mL						
Baseline	715 (23.8)	646 (22.8)	665 (22.9)	779 (26.5)	693 (23.4)	683 (23.9)
6 mo	958 (32)	611 (23.0)	793 (31)	621 (21)	885 (32)†	613 (22)‡
TLC,* mL						
Baseline	8,230 (153)	7,800 (142)	7,790 (176)	7,290 (118)	8,030 (164)	7,660 (130)
6 mo	7,337 (126)	7,624 (134)	6,632 (121)	7,319 (126)	7,037 (123)†	7,543 (131)‡
RV,* mL						
Baseline	5,469 (247)	5,388 (257)	5,678 (280)	4,900 (221)	5,563 (262)	5,250 (247)
6 mo	4,300 (193)	5,338 (249)	4,093 (200)	4,838 (216)	4,212 (196)†	5,205 (240)‡
$PaCO_2$,§ mm Hg						
Baseline	45.93 (7.05)	56.46 (8.66)	43.88 (7.47)	42.46 (6.2)	45.00	44.62 (8.08)
6 mo	43.79 (8.53)	46.36 (8.21)	39.89 (7.80)	44.71 (4.03)	42.1‖	45.9‡
DLCO,§ mL/min/mm Hg						
Baseline	8.23 (3.70)	8.71 (3.40)	6.71 (2.34)	8.42 (2.57)	7.58 (3.24)	8.63 (3.15)
6 mo	9.78 (4.45)	7.25 (5.35)	7.22 (2.0)	8.20 (3.4)	8.69‖	7.51‡
6MWD, feet						
Baseline	1,125 (362)	1,051 (283)	1,017 (300)	1,231 (312)	1,077 (337)	1,102‖ (299)
6 mo	1,278 (361)	1,053 (321)	1,158 (285)	1,148 (413)	1,223‖ (331)	1,041 (348)‖

*Values in parentheses are % predicted.
†$p < 0.01$.
‡Difference not significant.
§Values in parentheses are SD.
‖$p < 0.05$.

and 28% became worse. In the medical arm of the combined group, the performance of 25% of the patients improved, and 67% became worse. The difference between the two arms of the study reached statistically significant levels ($p = 0.001$) [Table 6].

Quality-of-Life Measures: At the 6-month follow-up time, all domains of the CRDQ showed better results in the LVRS arm than in the medical arms of the CLVR study, the OBEST, and the combined population (Table 7). The improvements in CRDQ scores were statistically significant in all four domains of the combined population. Similarly, the physical component summary scale score of the SF-36 showed a better outcome in the LVRS than in the medically treated cohort of the combined population. The mental component summary scale score demonstrated no significant difference between the two arms of the study. The less sensitive and generic SF-36 instrument demonstrated better outcomes in the surgical arms than in the medical arms in three of the eight domains. The most pronounced difference was a 26-point gain in the physical function domain ($p < 0.001$).

Comments

This study presents information on the therapeutic value of LVRS for patients who were enrolled in two separate but comparable randomized clinical trials. The data reveal that, in carefully selected patients with advanced heterogeneous (97.8% of total population)

Table 5—*Outcome Differences Between Surgical and Medical Arms 6 Months After Randomization**

Outcome	CLVR Study		OBEST		Combined			
	LVRS vs Medical	p Value	LVRS vs Medical Therapy	p Value	Weighted Mean Difference	Lower 95% CI	Upper 95% CI	p Value
FEV_1, mL	246	0.036	113	0.2327	167	29	304	0.017
TLC, mL	− 959	0.010	− 1,111	0.0019	− 1,044	− 1,483	− 605	< 0.001
RV, mL	− 1,379	0.0027	− 1,316	0.0012	− 1,342	− 1,844	− 840	< 0.001
PCO_2, mm Hg	− 4.80	0.030	− 4.82	0.5936	− 3.7183	− 6.960	− 0.477	0.025
DLCO, mL/min/mm Hg	1.615	0.067	− 0.2137	0.8535	0.9810	− 0.334	2.296	0.144
6MWD, feet	170.0	0.066	125.5	0.190	148.8	24.3	273.2	0.019

*Values were adjusted for blocking.

Table 6—*Stratification of 6MWD Results in Individuals 6 Months Postrandomization

Randomization/Results	CLVR Patients No.	%	OBEST Patients No.	%	Combined Patients No.	%
LVRS (n = 54)						
Better*	20	67	13	54	33	61
Worse or unchanged	7	23	9	38	16	30
Missing	3	10	2	8	5	9
Med Therapy (n = 39)						
Better*	6	21	4	36	10	26
Worse or unchanged	20	71	6	55	26	67
Missing	2	8	1	9	3	7
p Value	0.001		0.535		0.001	

*Better = > 100-foot increase from baseline level.

upper lobe emphysema, pulmonary function, exercise tolerance, and quality-of-life measures had improved 6 months after patients had undergone LVRS combined with optimal medical therapy, and were superior to those observed in patients who received optimal medical therapy alone. These results are consistent with findings in five other small randomized clinical trials,[5–9] in the "predominantly upper lobe emphysema-low exercise tolerance" cohort of the NETT[11] and in scores of observational studies.[22,23]

Selection criteria, baseline demographics, and outcomes were comparable in the CLVR study and the OBEST, so that the ingredients of the two trials were comparable and suitable for the analysis presented in this article. The surgical arm of the OBEST had a preponderance of women, but there is no suggestion in the literature that this gender disparity would alter outcomes.

Presently available information indicates that the selection criteria employed in the CLVR study and the OBEST represent reliable predictors of patient suitability for LVRS. Major deviations from these predictors can be fraught with serious consequences and are exemplified by the high operative mortality rate (15 to 25%), modest functional improvements, and lack of survival benefits reported by the NETT[24] in patients with an FEV_1 of ≤ 20% that was associated with either homogeneous emphysema and/or a DLCO of ≤ 20%. These features reflect severe and diffuse destruction of lung tissue, and have been associated with a predictably high risk for and limited benefits from LVRS.

The present report focuses on the 6-month outcome from LVRS. The Steering Committees of the OBEST thought that randomization for > 6 months could deprive patients in the medical arm of a promising palliative measure for an unduly long period of time, and that this represented grounds for ethical concerns.

Both the CLVR study and the OBEST focused on the palliative influence of LVRS without examining the impact of the operation on survival, since a fundamental tenet of medical therapeutics is that palliation, especially in patients with severe debilitating illnesses, can be as important as extending life span. The severity of the disability in patients with advanced emphysema certainly justifies performing a procedure that palliates symptoms and may not increase survival.

The 6-month mortality rate was similar in the medical and surgical arms of the combined CLVR study/OBEST population. This suggests that the

Table 7—*Differences in Quality-of-Life Scores Between Surgical and Medical Arms 6 Months Postrandomization*

Instrument	CLVR Surgery vs Medical	p Value	OBEST Surgery vs Medical	p Value	Combined Population Weighted Mean Difference	Lower 95% CI	Upper 95% CI	p Value
CRDQ								
Dyspnea	1.46	0.006	1.73	0.017	1.56	0.80	2.32	< 0.001
Fatigue	1.13	0.006	1.22	0.010	1.17	0.62	1.71	< 0.001
Mastery	1.36	0.002	0.96	0.041	1.19	0.63	1.74	< 0.001
Emotion	1.15	0.007	0.42	0.406	0.87	0.28	1.46	0.004
SF-36								
Physical functioning	28.80	< 0.001	20.75	0.052	25.94	14.36	37.52	< 0.001
Role physical	11.30	0.363	16.20	0.412	12.70	− 7.45	32.84	0.217
Bodily pain	− 2.70	0.776	− 2.94	0.781	− 2.80	− 16.43	10.82	0.687
General health	12.83	0.026	20.88	0.043	14.80	5.62	23.98	0.002
Vitality	5.51	0.310	20.61	0.022	10.00	1.30	18.71	0.024
Social functioning	11.44	0.324	4.11	0.747	8.13	− 8.35	24.62	0.334
Role emotional	− 28.81	0.055	18.98	0.310	− 10.40	− 32.31	11.52	0.352
Mental health	4.07	0.455	9.19	0.112	6.58	− 0.91	14.07	0.085
Physical component	7.48	0.003	4.35	0.383	6.90	2.86	10.94	< 0.001
Mental component	− 3.28	0.361	4.44	0.369	− 0.56	− 6.11	4.99	0.844

operative mortality rate in the LVRS arm was compensated, in a relatively short span of time, by deaths in the medical arm due to the natural progression of the disease. As the sample size for the present analysis was small, the premise is tentative, but it is supported by similar survival statistics in the predominantly upper lobe emphysema-low exercise tolerance cohort of the NETT. In that study, the 90-day mortality rates were similar in the medical and surgical cohorts, but after 29 months of follow-up the LVRS arm showed impressive survival advantages. It is possible that on longer follow-up patients in the surgical arm of the present study would show better survival than those in the medical arm.

The data presented in this communication also confirm the soundness of the volume reduction principle for emphysema of the lung, as the results show that LVRS provides measurable physiologic improvements and affords effective palliation. The results of observational studies[22,23] and the NETT randomized trial also suggest that the clinical and physiologic improvements peak 6 to 12 months after the LVRS and are sustained for 2 or 3 years before a serious decline in benefits is observed. Thus, the 6-month results from LVRS reflect the midterm palliative influence of the procedure. Available medical evidence also indicates that continued questioning of the therapeutic value of LVRS is no longer relevant, and that the debate about utilization of LVRS should shift from the medical aspects to economic and ethical concerns.[23] The economic question is about the monetary value of $\geq$ 2 years of freedom from a disabling disease. The ethical question is simply how long a palliation is long enough to justify the high cost of a therapeutic procedure.

There are slight differences in some outcome variables between the CLVR study and the OBEST, but the directions of outcome changes are the same and the differences between the two studies are not statistically significant. The small number of patients in each trial, the subtle differences in patient selection, the unappreciable disparity in rehabilitation programs or medical therapy, and the slight variations in surgical technique might have caused this apparent difference in results. It is probable that these minor disparities would decrease with larger patient enrollments.

Although demographic profiles, severity of illness, treatment provided, and the results obtained were similar in the CLVR study and the OBEST, hospital admissions were more frequent and hospital stays were longer in the CLVR study than in the OBEST. These differences most likely relate to a greater emphasis on reducing hospital utilization in the United States than in Canada, rather than to true differences in the character of patients, the quality of care, and the outcomes from treatment.

The modest mortality rate and the considerably higher morbidity rate, combined with the large economic cost associated with LVRS, represent major shortcomings of the procedure. Advances in technology hold the prospect of achieving lung volume reduction at much lower human and financial costs. Indeed, several different minimally invasive, bronchoscopic lung volume reduction methods are being evaluated at the present time. Encouraging results from animal studies[26,27] have been reported, but the outcome in humans has been inconsistent.

The shortcomings inherent in randomized clinical trials of complex surgical procedures are compounded by commonly encountered problems with patient recruitment and the relatively small populations that are available for analysis. The material presented in this communication suffers from these shortcomings in addition to having to combine data from two independent studies. We think that the conclusions obtained from this analysis are valid and relevant to the utilization of lung volume reduction operations. It is also relevant that the present study provides information from the second largest population available in the medical literature about randomized trials on LVRS. The authors appreciate that using the meta-analysis format may not be the ideal approach, but we think that it is a fair way to combine the data from two studies and to assess the results from a larger combined population.

Each of the 10 participating institutions in CLVR study and the OBEST performed fewer than a dozen LVRS operations under the aegis of the present clinical trials. Nonetheless, the functional results of operative mortality and morbidity were similar at the different clinical sites of the two studies and were comparable to those reported from medical centers with greater experience. This observation suggests that good results from LVRS can be obtained in qualified tertiary institutions and that the performance of the procedure need not be limited to a small number of highly specialized centers. It must be emphasized, however, that LVRS is a high-risk operation, and that the achievement of satisfactory results requires pulmonologists and thoracic surgeons who have adequate experience with performing LVRS, and up-to-date operating and intensive care facilities staffed by multidisciplinary teams that include anesthesiologists, critical care specialists, and respiratory therapists. The results will be disappointing if LVRS is performed for inappropriate indications, with inadequate experience, or by unqualified teams without appropriate facilities.

The present study indicates that, compared to optimal medical therapy, quality of life, symptoms of

dyspnea, pulmonary function, and exercise tolerance are improved 6 months after LVRS in patients with severe pulmonary emphysema. LVRS is an effective palliative intervention.

Appendix: CLVR-OBEST Study Group

CLVR Trial Centers

McMaster University, St Joseph's Healthcare Hamilton, ON; University of Western Ontario, London Health Sciences Centre London, ON; University of British Columbia, Vancouver General Hospital, Vancouver, BC; University of Manitoba., St Boniface Hospital Winnipeg, MB.

CLVR-Hamilton Center: Principal Investigators: John Miller and Charles Goldsmith; Investigators: David Stubbing, David Higgins, Gerry Cox; Michael Gent, Gary Foster, and Lori Edey; Pastoral Counselors: Bernie J. O'Brien, Roman Jeaschke, George Torrance, Allan Kitching, and Stuart Pugsley; National Research Trial Coordinators: Yasmin Sivji, Toni Newman, and Anne Moore-Cox; Local research trial coordinator: Ellen MacDonald; Blinded QOL Assessors: Sarah Goodwin and Eleanor Kent; and secretary: Estelle Richards.

London Health Sciences Center: Principal Investigator: Richard Malthaner; Investigator: Sanjay Mehta; Coordinator and QOL Assessor: Deb Lewis; Coordinator: Deb Fenlon; Blinded QOL assessor: Diane Jamieson; and secretary: Dell Walker.

Winnipeg: Principal Investigator, Lawrence Tam; and Coordinators: Steven Mink and Cindy Dudar.

Vancouver: Principal Investigator: Jeremy Road; Local Research Trial Coordinators: Ken Evans, Richard Finley, Guy Fradey, Robert Levy, Richard Pardy, Pat Camp, Carol Storseth, and Marliese Dawson; Blinded QOL Assessor: Baljit Samrai; and secretary: Filomena Greenslade.

OBEST Centers

Bay State Medical Center, Beth Israel Deaconess Medical Center, Boston Medical Center, Brigham and Women's Hospital, Lahey Clinic, Massachusetts General Hospital, Newton Wellesley Hospital, North Shore Medical Center, Saints Memorial Medical Center, St. Elizabeth's Medical Center, and U Mass-Memorial Hospitals.

Medical School Affiliations: Boston University School of Medicine, Harvard Medical School, Tufts Medical School, and University of Massachusetts Medical School.

OBEST Leaders: Project Director: Robert L. Berger; Medical Advisor: Anne L. Meneghetti; Principal Advisor: Gordon L. Snider; Scientific Advisor: Bartolome R. Celli; and Consultant: Evelyn Murphy.

Principal and Co-Principal Investigators of OBEST: P. H. Bagley, UMass/Memorial Health Care; D.J. Beer, Newton Wellesley Hospital; I. Buchwald, Saints Memorial Medical Center; B. Celli and J. Stetz Jr., St. Elizabeth's Medical Center; A. W. Gray, C. Williamson, Lahey Medical Center; F. M. Hasan and S. Neil, North Shore Medical Center; E. M. Ingenito and S. J. Mentzer, Brigham & Women's Hospital; J. N. Landis, Bay State Medical Center; J. LoCicero and R. Silvestri, Beth Israel-Deaconess Medical Center; C. D. Wright, Massachusetts General Hospital.

DCC: Donna Danielewsky, E. Poggio, and D. Amato, Abt Associates; H. Golub, C. Hall, S. Hamer, and S. Brouwer, CareStat Inc.; and T. McLoud, Imaging Center, Massachusetts General Hospital.

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