

EFFECT OF LUNG-VOLUME-REDUCTION SURGERY IN PATIENTS WITH SEVERE EMPHYSEMA

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ABSTRACT

Background Although many patients with severe emphysema have undergone lung-volume-reduction surgery, the benefits are uncertain. We conducted a randomized, controlled trial of the surgery in patients with emphysema. Patients with isolated bullae were excluded because such patients are known to improve after bullectomy.

Methods Potentially eligible patients were given intensive medical treatment and completed a smoking-cessation program and a six-week outpatient rehabilitation program before random assignment to surgery or continued medical treatment. After 15 patients had been randomized, the entry criteria were modified to exclude patients with a carbon monoxide gas-transfer value less than 30 percent of the predicted value or a shuttle-walking distance of less than 150 m, because of the deaths of 5 such patients (3 treated surgically and 2 treated medically).

Results Of the 174 subjects who were initially assessed, 24 were randomly assigned to continued medical treatment and 24 to surgery. At base line in both groups, the median forced expiratory volume in one second (FEV₁) was 0.75 liter, and the median shuttle-walking distance was 215 m. Five patients in the surgical group (21 percent) and three patients in the medical group (12 percent) died (P=0.43). After six months, the median FEV₁ had increased by 70 ml in the surgical group and decreased by 80 ml in the medical group (P=0.02). The median shuttle-walking distance increased by 50 m in the surgical group and decreased by 20 m in the medical group (P=0.02). There were similar changes on a quality-of-life scale and similar changes at 12 months of follow-up. Five of the 19 surviving patients in the surgical group had no benefit from the treatment.

Conclusions In selected patients with severe emphysema, lung-volume-reduction surgery can improve FEV₁, walking distance, and quality of life. Whether it reduces mortality is uncertain. (N Engl J Med 2000;343:239-45.)

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LUNG-volume-reduction surgery has been performed in thousands of people with emphysema in recent years.¹ More than 30 separate reports of over 2000 operations have found substantial and clinically relevant improvements in lung function, walking distance, and quality of life.²⁻⁸ Nevertheless, the clinical benefits of the procedure have been questioned; private insurers and

governmental organizations have refused to pay for the operation. The American Thoracic Society, together with others, has emphasized the need for randomized, controlled trials.⁹⁻¹² Such trials are needed for several reasons. First, patient selection and methods of rehabilitation may affect the apparent improvements associated with surgery. Second, surgery may produce an initial improvement at the cost of a subsequent accelerated decline. Third, some series have included patients with bullae, whose condition is known to improve after bullectomy. Fourth, there is substantial operative morbidity, and reported operative mortality varies from 0 to 19 percent.¹⁻⁷ Finally, lung-volume-reduction surgery is expensive, and there are many millions of potential candidates. A true comparative analysis is therefore needed, with a control group randomly assigned to receive the same intensive rehabilitation and medical management as that given to the patients who undergo surgery.

From April 1996 through February 1999, we enrolled patients with emphysema but without isolated bullae in a randomized, controlled trial of lung-volume-reduction surgery. We report the results for 48 patients who were followed for periods ranging from 6 to 12 months.

METHODS

Trial Design

Patients were enrolled between April 1996 and February 1999. They were referred by specialist pulmonary physicians to be considered for lung-volume-reduction surgery in the context of a randomized, controlled trial. Patients were informed about the trial and the risks and benefits of surgery. The entry criteria were severe emphysema, as shown on computed tomography (CT), with no restriction on the pattern or distribution of the emphysema; an age of less than 75 years; a forced expiratory volume in one second (FEV₁) greater than 500 ml; use of oxygen for less than 18 hours per day; a corticosteroid dose of less than 10 mg per day; and a partial pressure of arterial carbon dioxide of less than 45 mm Hg. Patients with asthma, previous thoracic surgery, or other serious medical conditions were excluded.

The patients were given medical treatment consisting of a smoking-cessation program; trial therapy with prednisolone (30 mg per day for two weeks); inhaled beta-adrenergic agonists and anticholinergic drugs at optimal doses; oral theophylline, with the response judged on the basis of symptoms and spirometric measures; oral antibiotics to be kept at home for use when needed for chest infections; and vaccination against influenza and pneumococcus.

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Patients without any clear contraindications on initial assessment were entered into a six-week program of outpatient rehabilitation, consisting of physiotherapy and occupational therapy, with nursing, dietetic, and social services. Physiotherapy included graded walking, arm and leg exercises, and thoracic-mobility exercises. Occupational therapy consisted of stress management, advice on energy conservation, and work advice. Patients were contacted by telephone regularly by their physiotherapists for assessment and to encourage adherence to the rehabilitation program.

After rehabilitation the patients were reassessed by the trial physicians. Those wishing to proceed were assessed by a surgeon, together with a physician and a physiotherapist, to confirm their suitability for surgery and were then randomly assigned to surgery or to continued medical treatment. Both groups were reassessed 3, 6, and 12 months after randomization and at yearly intervals thereafter. The patients assigned to medical treatment were told that they would be offered surgery if the trial showed a significant benefit of surgery after the interim or final analysis. An independent data-monitoring committee was set up to conduct the interim analysis and advise on the subsequent conduct of the trial.

Five of the first 15 patients (3 assigned to surgery and 2 to medical treatment) died early in the trial. These patients had carbon monoxide gas-transfer values less than 30 percent of the predicted value or shuttle-walking distances of less than 150 m (see below), whereas survivors had higher values. The entry criteria were subsequently modified to exclude patients with these low values for carbon monoxide gas transfer or walking distance.

Initial Assessment and Follow-up

The patients were interviewed and examined to evaluate their mobility, general health, smoking status, and willingness to participate. Pulmonary-function testing consisted of measurements of FEV₁, forced vital capacity, single-breath carbon monoxide gas transfer, arterial-blood gases, total lung capacity, residual volume (by whole-body plethysmography), and maximal inspiratory and expiratory mouth pressures. Exercise tolerance was assessed by the shuttle-walking test, as validated by use in patients with chronic lung disease.¹³ This test measures the distance walked on a level surface when the patient is asked to walk at set speeds that increase after each 10 m.

Imaging consisted of chest radiography and CT scanning (with an electron-beam scanner; Imatron, South San Francisco, Calif.), including inspiratory and expiratory thin sections and contiguous 10-mm sections at full inspiration.

Echocardiography, electrocardiography, thallium scanning, and standard biochemical and hematologic tests were performed in all subjects. Smoking status at enrollment and at randomization was tested by measurement of urinary cotinine. Quality of life was assessed with use of the 36-item Short-Form Health-Related Questionnaire (SF-36), in which the score ranges from 0 (indicating low quality) to 100 (indicating high quality).¹⁴

Lung function, shuttle-walking distance, and quality of life were assessed 3, 6, 12, and 24 months after randomization to medical or surgical treatment.

Outcome Measures

The primary outcome measures were mortality and changes in FEV₁, shuttle-walking distance, and quality of life at six months. The secondary outcome measures were: changes in forced vital capacity, total lung capacity, residual volume, inspiratory and expiratory mouth pressures, and arterial-blood gas values.

Surgery

Bilateral lung resection was performed through median sternotomy or by thoracoscopy. Lung resection was performed with the use of various mechanical staplers, with or without bovine-pericardial-strip reinforcement. The site and extent of resection were decided on the basis of CT scanning, together with the findings at surgery. Air leaks were prevented by the use of Tisseal (human fibrin glue), if required. Pleurodesis was not performed, but

a pleural tent was fashioned to minimize air leak. Anesthesia was induced and maintained with propofol, and a lumbar or thoracic epidural infusion of diacetylmorphine was instituted. The patient underwent extubation immediately after recovering consciousness at the end of the procedure, with permissive hypercapnia during artificial ventilation. Postoperative analgesia was maintained with the epidural infusion. Standard prophylactic treatment included antibiotics and subcutaneous low-molecular-weight heparin.

Statistical Analysis

Statistical calculations based on a mean (\pm SD) FEV₁ of 0.9 \pm 0.4 liter showed that 50 patients would be required to demonstrate a 30 percent difference after six months with a power of 90 percent (with a type I error of 0.05) in a between-group comparison.¹³ An independent institute (Clinical Trials Unit, Institute of Cancer Research, England) performed the randomization. The patients were stratified according to their FEV₁ values (at least 0.75 liter or less than 0.75 liter) and the presence or absence of α_1 -antitrypsin deficiency as determined by serum immunoturbidometry.

Categorical variables were analyzed by Fisher's exact test.¹⁵ Comparisons between the two groups were performed by the Wilcoxon rank-sum test.¹⁵ We tested whether changes from base line were significantly different from zero within each group by using the Wilcoxon matched-pairs signed-rank test.¹⁵ Mortality rates in the two groups were compared with use of life-table analysis with a log-rank test. Relative risks of death at all time points were obtained with use of Cox's regression model. The vital status of each patient through the end of May 1999 was ascertained. Analyses were performed with the statistical software packages SAS and Stata. The results are shown for all patients unless otherwise specified and are expressed as median values with interquartile ranges. All reported P values are for two-sided tests. The trial was approved and monitored by the Royal Brompton Hospital research ethics committee, and all patients gave written informed consent.

RESULTS

Recruitment

One hundred seventy-four patients were referred, and 48 were randomly assigned to treatment, 24 to each group. The reasons for exclusion were low results on tests of lung function or walking distance (78 patients), reluctance to take part in the study (32 patients), other lung disease (8 patients), continued smoking (5 patients), and geographic or other reasons (3 patients). After randomization, one patient in the surgical group withdrew from the trial before surgery. The base-line characteristics of the patients, including the distribution of emphysema on CT, did not differ significantly between the groups (Table 1). Six patients in the medical group (25 percent) and seven in the surgical group (29 percent) were women. The median age was 60 years (interquartile range, 53 to 69) for medically treated patients and 62 years (interquartile range, 56 to 67) for surgically treated patients. Among the medically treated patients, the distribution of emphysema according to CT scanning was generalized in 12 patients, predominantly in the upper zone in 9, and predominantly in the lower zone in 3. Among the surgically treated patients, the corresponding numbers were 14, 8, and 2 patients.

Primary Outcomes

There were five deaths in the surgical group (21 percent) and three in the medical group (12 per-

TABLE 1. OUTCOME MEASURES AT BASE LINE AND AFTER LUNG-VOLUME-REDUCTION SURGERY OR CONTINUED MEDICAL TREATMENT.*

CHARACTERISTIC	BASE LINE			3 MO			6 MO			12 MO		
	MEDICAL GROUP (N=24)	SURGICAL GROUP (N=24)	P VALUE	MEDICAL GROUP (N=23)	SURGICAL GROUP (N=19)	P VALUE	MEDICAL GROUP (N=23)	SURGICAL GROUP (N=19)	P VALUE	MEDICAL GROUP (N=19)	SURGICAL GROUP (N=13)	P VALUE
FEV ₁ (liters)†												
Median	0.75	0.74	0.87	0.70	0.91	0.02	0.72	0.92	0.09	0.74	0.84	0.45
Interquartile range	0.66–0.93	0.61–0.97		0.61–0.92	0.75–1.36		0.65–0.90	0.68–1.28		0.65–0.87	0.67–0.96	
Shuttle-walking distance (m)†												
Median	220	210	0.93	230	260	0.46	210	270	0.44	205	290	0.26
Interquartile range	185–290	180–280		180–330	200–350		180–330	200–360		140–330	150–400	
SF-36 score‡‡												
Median	50	51	0.56	46	57	0.07	43	72	<0.001	42	72	0.01
Interquartile range	40–59	48–56		37–54	48–69		29–52	61–78		28–55	59–86	
FVC (liters)												
Median	2.81	2.91	0.93	2.53	2.84	0.26	2.58	2.96	0.11	2.68	2.78	0.38
Interquartile range	2.47–3.44	2.29–3.38		2.07–3.78	2.46–4.20		2.04–3.39	2.42–4.26		2.09–3.06	2.48–3.38	
Residual volume (% of predicted)												
Median	220	226	0.79	229	169	<0.001	228	163	<0.001	233	171	0.02
Interquartile range	201–255	200–255		205–284	151–190		204–281	133–202		206–263	156–226	
Total lung capacity (% of predicted)												
Median	129	136	0.23	133	119	0.005	139	119	0.002	127	126	0.17
Interquartile range	120–143	129–143		120–146	101–126		118–144	105–127		116–146	98–134	
PaCO ₂ (mm Hg)												
Median	38	37	0.78	37	38	0.47	38	37	0.39	38	41	0.70
Interquartile range	35–40	34–41		34–41	35–40		35–44	34–40		37–43	37–42	
PaO ₂ (mm Hg)												
Median	70	74	0.36	75	76	0.92	73	71	0.92	68	77	0.08
Interquartile range	66–78	68–80		66–80	69–80		65–77	67–80		64–76	66–83	
Carbon monoxide diffusing capacity (% of predicted)												
Median	37	36	0.66	36	42	0.68	37	42	0.32	35	45	0.11
Interquartile range	33–49	30–46		29–49	32–46		33–50	39–48		31–50	38–49	
Mouth inspiratory pressure (cm of water)												
Median	68	64	0.41	62	83	0.04	58	80	0.02	63	75	0.02
Interquartile range	51–78	53–69		51–76	49–89		44–74	61–95		57–70	68–82	
Mouth expiratory pressure (cm of water)												
Median	81	69	0.46	76	70	0.14	74	69	0.33	71	66	0.44
Interquartile range	54–96	54–79		70–89	58–79		60–100	53–87		66–92	50–96	

*The Wilcoxon rank-sum test was used for all analyses. FEV₁ denotes forced expiratory volume in one second, FVC forced vital capacity, PaCO₂ partial pressure of arterial carbon dioxide, and PaO₂ partial pressure of arterial oxygen.

†Values are primary outcome measures.

‡SF-36 denotes the 36-item Short-Form Questionnaire, on which scores range from 0 (indicating a low quality of life) to 100 (indicating a high quality of life).

cent). The operative mortality (in-hospital deaths after surgery) was 6 percent (1 of 18) among those who met the modified criteria and 17 percent (4 of 23) overall, not including the patient who withdrew after assignment to surgery. The early deaths in the surgical group (on days 2, 11, 15, and 74 after surgery) were due to respiratory failure, with or without infection. One other surgically treated patient died suddenly at home 287 days after surgery. Deaths in the medical group (on days 72, 242, and 475 after

randomization) were due to respiratory failure. Analysis of the entire study group showed no significant difference in survival between groups (relative risk of death in the surgical as compared with the medical group, 1.74; 95 percent confidence interval, 0.47 to 6.46; $P=0.29$, by the log-rank test).

The median changes in FEV₁, shuttle-walking distance, and SF-36 scores from base line to months 3, 6, and 12 are shown in Figures 1 and 2. These changes were calculated for patients who had both sets of

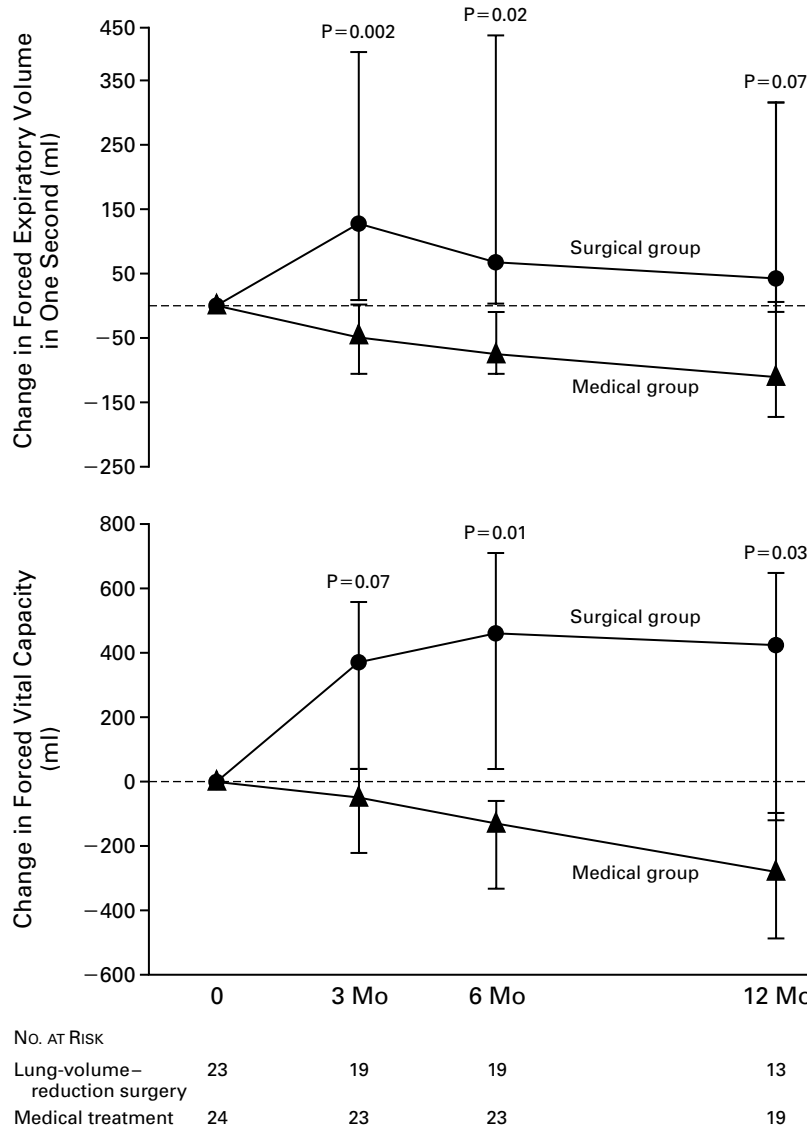


Figure 1. Median Changes in Forced Expiratory Volume in One Second and Forced Vital Capacity in the Groups Receiving Surgical and Medical Treatment.

The median changes were obtained by comparing the responses of each subject with his or her base-line values, and they therefore differ from the values shown in Table 1. P values are for the comparison between the two groups at each time point. I bars show 95 percent confidence intervals.

measures (i.e., for survivors at each time point) and are therefore not identical to the values shown in Table 1. The values improved in the surgical group and tended to worsen in the medical group. The changes from base line differed significantly between the medical and surgical groups at 6 months for FEV₁ (-80 ml and +70 ml, respectively; P=0.02), shuttle-walking distance (-20 m and +50 m, P=0.02), and SF-36 scores (-12 and +22, P=0.003); for FEV₁ at 3 months; and for shuttle-walking distance and SF-36 score at 12 months.

Secondary Outcomes

The median changes in forced vital capacity, percentage of predicted total lung capacity, and percentage of predicted residual volume from base line to months 3, 6, and 12 are shown in Figures 1 and 3. These changes were calculated for patients who had both sets of measures (i.e., for survivors at each time point) and are therefore not identical to the values shown in Table 1. All differences between the surgical and the medical groups were significant, except that forced vital capacity did not differ signifi-

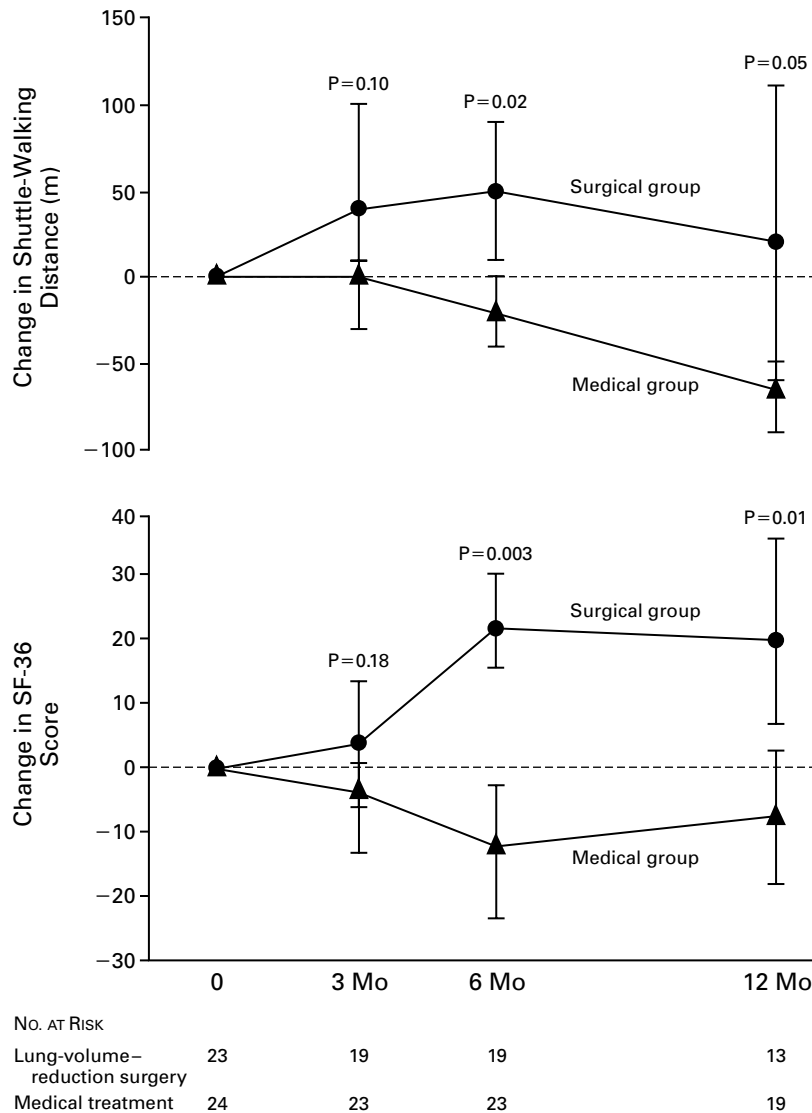


Figure 2. Median Changes in Shuttle-Walking Distance and Score on the 36-Item Short-Form Questionnaire (SF-36) Measuring Quality of Life in the Groups Receiving Surgical and Medical Treatment. The median changes were obtained by comparing the responses of each subject with his or her baseline values, and they therefore differ from the values shown in Table 1. P values are for the comparison between the two groups at each time point. The SF-36 score ranges from 0 (indicating a low quality of life) to 100 (indicating a high quality of life). I bars show 95 percent confidence intervals.

cantly between the groups at three months. The value for inspiratory mouth pressure, a measure of diaphragm function, increased in the surgical group and decreased in the medical group. There were no other significant changes in secondary outcomes.

Five of the 19 surviving surgically treated patients had no benefit after surgery. None of the patients resumed smoking. These patients had base-line characteristics similar to those of the patients who showed

improvement after surgery, except that their emphysema was more diffusely distributed according to CT scanning. In the surgical group, the mean hospital stay was 19 days (range, 8 to 64). Postoperative complications included persistent air leak in three patients and infection in two patients.

After analysis of the results, the 21 patients in the medical group who completed at least six months of the trial were reassessed. Eight no longer met the

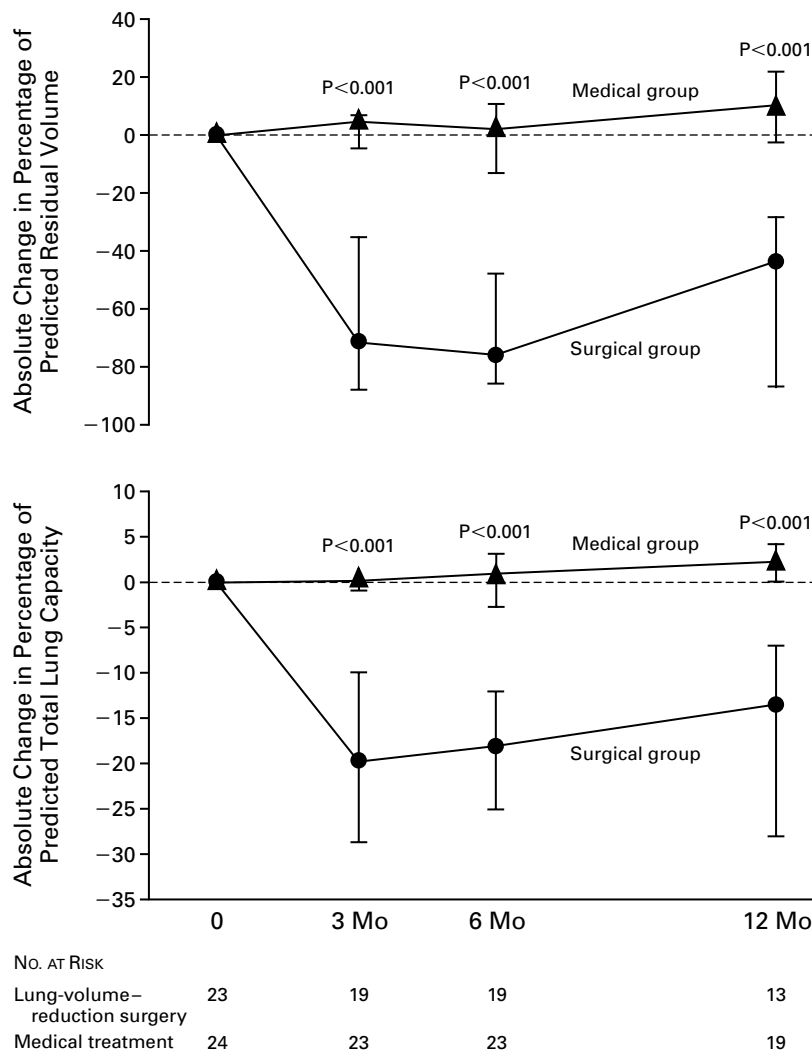


Figure 3. Median Absolute Changes in Residual Volume and Total Lung Capacity, as a Percentage of the Predicted Value, in the Groups Receiving Surgical and Medical Treatment. The median changes were obtained by comparing the responses of each subject with his or her baseline values, and they therefore differ from the values shown in Table 1. P values are for the comparison between the two groups at each time point. I bars show 95 percent confidence intervals.

criteria for surgery because of a decline in lung function, five no longer wanted to be considered for surgery, and eight were offered surgery. Six underwent surgery. All six patients were alive 3 to 10 months after surgery. FEV₁ improved by a mean of 0.27 liter; two of the six patients had no clinical benefit.

DISCUSSION

In a randomized, controlled trial, we found statistically significant benefits in terms of FEV₁, shuttle-walking distance, and quality of life at various follow-up times. Mortality was similar in the two groups,

but the study had too few patients for us to evaluate this end point adequately. Although most patients who underwent surgery had considerable benefit, a few did not. In contrast, the condition of most of the patients treated medically got worse. We therefore consider these changes to be clinically significant for the surgical group as a whole.

A review of 722 patients who underwent lung-volume–reduction surgery between October 1995 and January 1996 showed that 12 months after surgery, 23 percent had died.¹² Our results are similar. Nevertheless, the mortality early in our trial was un-

acceptably high, and therefore the entry criteria were modified. These early operative deaths may have been in part attributable to the inexperience of the surgical team as well as to the severity of the patients' emphysema.

The rate of decline in lung function after randomization was similar in the two groups, with a yearly decrease of 100 ml in FEV₁. This result suggests that surgery produced a one-time benefit but did not modify the subsequent natural history of the disease. The rate of decline in our patients was higher than the average for ex-smokers with chronic obstructive pulmonary disease but similar to that reported in another study of lung-volume-reduction surgery.¹² This is not surprising, given the fact that more severely affected patients are selected for the operation.

The chief weaknesses of this study were the small number of patients enrolled and the need to modify the entry criteria after the first 15 patients had undergone randomization. The number of patients was limited for two reasons. First, there was reluctance on the part of referring physicians and patients alike to be subjected to the uncertainty of randomization, particularly in the face of reports about the benefits of surgery. Many patients refused to participate, and some arranged to have surgery elsewhere. Second, all patients were told at entry that they would be offered the operation if the trial showed positive results. We therefore conducted an interim analysis and allowed patients assigned to medical treatment to proceed to surgery.

Although some centers have reported no deaths at all after lung-volume-reduction surgery, and others have had good results even in the most severely affected patients, the 6 percent mortality among our patients who met the modified entry criteria is in line with general experience. The reductions in total lung capacity and residual volume are also similar to those in other studies, whereas the changes in FEV₁ (an increase of 17.6 percent at three months and 9.5 percent at six months) are at the lower end of reported benefits. This is likely to reflect in part our rigid exclusion of patients with isolated bullae, for whom surgery has a well-established role. The inclusion of such patients in previous reports may account for the more remarkable successes of up to 80 percent improvement in FEV₁. During the period of this trial, seven patients with localized bullae underwent bullectomy at our institution (outside the trial); their mean FEV₁ rose from 1.22 to 1.98 liters (an increase of 62 percent). The substantial improvements in walking distance (19 percent at three months, and 24

percent at six months) and quality of life are similar to those found by others. They are probably due to changes in both lung and diaphragmatic function, but we recognize that the placebo effect of surgery may have played a part.

Our randomized, controlled trial has confirmed the benefits of lung-volume-reduction surgery that were suggested by other studies.^{16,17} Although only a small proportion of patients with chronic obstructive pulmonary disease may benefit from the surgery, their number may be large. The selection criteria need to be improved before the operation becomes routine.

Supported by research funding from the Royal Brompton Hospital.

We are indebted to Julia Bott for help in the design of the study.

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