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PATIENTS AT HIGH RISK OF DEATH AFTER LUNG-VOLUME-REDUCTION SURGERY

NATIONAL EMPHYSEMA TREATMENT TRIAL RESEARCH GROUP*

ABSTRACT

Background Lung-volume-reduction surgery is a proposed treatment for emphysema, but optimal selection criteria have not been defined. The National Emphysema Treatment Trial is a randomized, multicenter clinical trial comparing lung-volume-reduction surgery with medical treatment.

Methods After evaluation and pulmonary rehabilitation, we randomly assigned patients to undergo lung-volume-reduction surgery or receive medical treatment. Outcomes were monitored by an independent data and safety monitoring board.

Results A total of 1033 patients had been randomized by June 2001. For 69 patients who had a forced expiratory volume in one second (FEV₁) that was no more than 20 percent of their predicted value and either a homogeneous distribution of emphysema on computed tomography or a carbon monoxide diffusing capacity that was no more than 20 percent of their predicted value, the 30-day mortality rate after surgery was 16 percent (95 percent confidence interval, 8.2 to 26.7 percent), as compared with a rate of 0 percent among 70 medically treated patients ($P < 0.001$). Among these high-risk patients, the overall mortality rate was higher in surgical patients than medical patients (0.43 deaths per person-year vs. 0.11 deaths per person-year; relative risk, 3.9; 95 percent confidence interval, 1.9 to 9.0). As compared with medically treated patients, survivors of surgery had small improvements at six months in the maximal workload ($P = 0.06$), the distance walked in six minutes ($P = 0.03$), and FEV₁ ($P < 0.001$), but a similar health-related quality of life. The results of the analysis of functional outcomes for all patients, which accounted for deaths and missing data, did not favor either treatment.

Conclusions Caution is warranted in the use of lung-volume-reduction surgery in patients with emphysema who have a low FEV₁ and either homogeneous emphysema or a very low carbon monoxide diffusing capacity. These patients are at high risk for death after surgery and also are unlikely to benefit from the surgery. (N Engl J Med 2001;345:1075-83.)

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LUNG-volume-reduction surgery is a potentially valuable treatment for patients with advanced emphysema.¹⁻⁸ During the operation, 20 to 35 percent of the emphysematous lung is resected by means of either a median sternotomy or video-assisted thoracoscopy. Generally, lung function, exercise capacity, and the quality of life improve after surgery, but the results vary.⁹ The surgical mortality rate ranges from 4 to 15 percent,³ and one-year mortality rates are as high as 17 percent,¹⁰ although follow-up has often been incomplete.¹¹ A review of Medicare claims showed that the six-month mortality rate was 16.9 percent.¹² Uncertainty about the risk of lung-volume-reduction surgery, the magnitude and duration of benefit, and optimal selection criteria led the National Heart, Lung, and Blood Institute and the Center for Medicare and Medicaid Services (formerly the Health Care Financing Administration) to sponsor a multicenter, randomized clinical trial, the National Emphysema Treatment Trial.¹³

The main goal of the trial is to compare survival rates and exercise capacity two years after lung-volume-reduction surgery with the results obtained after medical treatment. An important goal of the trial is to identify selection criteria for lung-volume-reduction surgery. The inclusion criteria for the trial are broad enough to allow the evaluation of subgroups of patients who have traditionally been considered candidates for surgery, but who were present in only small numbers in previous studies.¹⁰ Every three months a

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data and safety monitoring board reviews recent medical literature, the quality of the data, adverse events, and outcome data from the trial. The board is charged with periodically reviewing subgroups of patients who may benefit from or be harmed by the procedure; as a result of such review, a set of clinical characteristics that defines a group of patients with a high mortality rate and little benefit after lung-volume-reduction surgery has been identified and is described in this article. The National Emphysema Treatment Trial has now modified the protocol to exclude these patients. Patients who do not meet these exclusion criteria continue to be enrolled in the trial, and their results will be reported when the trial is completed.

METHODS

The design and methods of the National Emphysema Treatment Trial have been described previously¹³ and are summarized below.

Screening and Base-Line Assessments

The inclusion criteria were as follows: a forced expiratory volume in one second (FEV₁) that was no more than 45 percent of the predicted value¹⁴ but that was at least 15 percent of the predicted value among patients who were 70 years of age or older, a total lung capacity that was at least 100 percent of the predicted value,¹⁵ a residual volume that was at least 150 percent of the predicted value,¹⁵ a partial pressure of arterial carbon dioxide of 60 mm Hg or less (55 mm Hg in Denver) while patients were at rest and breathing room air, a partial pressure of arterial oxygen of at least 45 mm Hg (30 mm Hg in Denver) while patients were at rest and breathing room air, an ability to walk farther than 140 m (459 ft) in six minutes, an ability to complete three minutes of pedaling on a bicycle ergometer without a load, and abstinence from smoking for six months before randomization. Patients had to complete a measurement of carbon monoxide diffusing capacity but were not excluded on the basis of the value.¹⁶ Lung function was tested according to the guidelines of the American Thoracic Society.¹⁷⁻¹⁹ Patients were excluded if they had other medical conditions that made them unsuitable for surgery or that might interfere with follow-up. All patients provided written informed consent, and the study was approved by the institutional review board at each center.

The severity and distribution of emphysema were determined from high-resolution computed tomographic (CT) scans of the chest obtained during full inspiration. Each lung was divided into three apical-to-basal zones, and each zone was scored visually by a radiologist who had been trained in the study protocol. The extent of emphysema was graded from 0 to 4, with a grade of 0 indicating no emphysema and a grade of 4 indicating the presence of emphysema in more than 75 percent of the lung zone.²⁰⁻²² Heterogeneous emphysema was defined as a difference in scores of at least two among the three zones in one lung; otherwise, the distribution of emphysema was classified as homogeneous.

The initial evaluation included six-minute walk tests,^{23,24} lung-function tests, bicycle ergometry to determine maximal exercise capacity, the 77-item Quality of Well-Being questionnaire (scores can range from 0 to 1, and higher scores indicate a better quality of life),²⁵ echocardiography, radionuclide pharmacologic (dobutamine) stress testing, measurement of arterial blood gases, and lung-perfusion scanning. Patients who met the enrollment criteria had to complete 6 to 10 weeks of pulmonary rehabilitation, after which the participating center's pulmonologist and surgeon, in consultation with an anesthesiologist and, if necessary, a cardiologist, had to determine whether the patient was a suitable candidate for lung-volume-reduction surgery. Exercise testing, lung-function testing, the Quality of Well-Being questionnaire, and six-minute walk testing were then repeated. Patients who were randomly assigned to medical therapy continued pulmonary rehabilitation and medical

treatment. Patients who were randomly assigned to undergo lung-volume-reduction surgery underwent bilateral surgery by means of either a median sternotomy or video-assisted thoracoscopy; the goal was to resect 20 to 35 percent of each lung. After surgery, patients continued rehabilitation and medical treatment. Pulmonary-function testing, exercise testing, the Quality of Well-Being questionnaire, and the six-minute walk test were repeated six months after randomization.

Statistical Analysis

We ascertained vital status as of June 2001. In the calculations of 30-day surgical mortality rates we included only patients who actually underwent lung-volume-reduction surgery within the trial. Other analyses were conducted according to the intention-to-treat principle and included patients in their assigned group regardless of the treatment received. We used contingency tables to estimate the relative risk of death between treatment groups, and we used the Poisson distribution to calculate 95 percent confidence intervals.²⁶ Kaplan-Meier survival curves from the date of randomization were compared with use of the log-rank test.²⁷ We compared functional outcomes in survivors of surgery and medically treated patients six months after enrollment using two-sample t-tests of the mean change from base line. To account for deaths and missing information, we used the following scoring system to define the change in functional outcome at six months: patients who had died were given a score of 0, patients who did not complete the evaluation were given a score of 1, and other patients were given a score ranging from 2 to 10, depending on the size of the change. For bicycle ergometry, patients who could not pedal for three minutes without a load were classified as unable to complete testing. Patients who had died were given a score of 0 on the Quality of Well-Being questionnaire. Patients who did not complete the questionnaire were assigned a value equal to one half the lowest score. We compared the distributions of scores between groups using the Wilcoxon rank-sum exact test.²⁸ All P values were two-sided.

Interim Monitoring

At the outset of the study, the investigators provided the data and safety monitoring board with stopping guidelines that were to be used to identify subgroups that benefited from lung-volume-reduction surgery as well as subgroups whose risk was increased by the procedure. Both the investigators and the data and safety monitoring board considered a 30-day surgical mortality greater than 8 percent to be unacceptable; a stopping guideline was therefore instituted to terminate randomization if the lower 95 percent confidence limit for 30-day mortality exceeded 8 percent.

The investigators requested that the data and safety monitoring board pay special attention to a subgroup of patients who were thought likely to have substantial benefit from lung-volume-reduction surgery, with the understanding that this group might have enrollment terminated early if such benefit were found. The criteria for the group thought likely to benefit were an age of 70 years or less, a postbronchodilator FEV₁ of 15 to 35 percent of the predicted value, a partial pressure of arterial carbon dioxide of 50 mm Hg or less (45 mm Hg in Denver), a residual volume greater than 200 percent of the predicted value, a low radionuclide perfusion ratio (0.2 or less), a heterogeneous pattern of emphysema on CT scanning, and evidence of hyperinflation on chest radiography.

The data and safety monitoring board examined these seven candidate variables and five other variables (the carbon monoxide diffusing capacity, maximal work capacity, quality of life, race or ethnic group, and sex) added by the investigators and approved by the data and safety monitoring board to identify subgroups of patients who might not benefit or might be at risk from lung-volume-reduction surgery. Exploratory analyses were conducted for each of these variables. Continuous measures were analyzed both on a continuous scale and in binary categories, dichotomized at the approximate quartile for the worst prognosis.

The data and safety monitoring board reviewed subgroups of patients derived with these candidate variables every three months

for evidence of increased risk or benefit from lung-volume-reduction surgery as compared with medical management. The statistical significance of the subgroup differences for each variable was determined from a test for interaction of the variable with treatment group, with a proportional-hazards regression model for overall mortality.

Identification of a High-Risk Group

In April 2001, these analyses suggested that a low FEV₁, a homogeneous pattern of emphysema, and a high perfusion ratio predicted an increased risk of overall mortality. In addition, a low FEV₁ and a low carbon monoxide diffusing capacity were associated with increased 30-day mortality. Additional analyses of patients with a low FEV₁ were then requested by the data and safety monitoring board to determine whether combination with the three other factors could define a subgroup of patients who exceeded the stopping guideline for 30-day mortality. The data and safety monitoring board, recognizing that any particular cutoff value for a continuous variable is inherently arbitrary, also requested sensitivity analyses varying the cutoff values for FEV₁ and carbon monoxide diffusing capacity. In May 2001, the data and safety monitoring board found that the subgroup defined by a combination of low FEV₁ and either homogeneous emphysema or low carbon monoxide diffusing capacity satisfied the stopping guidelines. Therefore, the data and safety monitoring board recommended stopping enrollment of these patients. The board also found that the perfusion ratio did not add prognostic value after the other risk factors had been accounted for. It further concluded that the selected thresholds for FEV₁ and carbon monoxide diffusing capacity were the best, given the available data.

Because several risk factors with many potential cutoff points were examined several times, the investigators and the data and safety monitoring board considered whether discovery of the high-risk subgroups might represent a type I error. We concluded, however, that the present findings are unlikely to represent a type I error. The risk factors were identified prospectively on the basis of experience and biologic information outside the trial and were examined with respect to stringent prespecified stopping criteria. In addition, longitudinal views of the data suggested consistency and increasing statistical significance over time before the actual decision point.

RESULTS

Between January 1998 and June 2001, 1033 patients underwent randomization at 17 clinical centers. One hundred forty of the patients (13.6 percent) were in the group at high risk for death after lung-volume-reduction surgery (70 in the group assigned to surgery and 70 in the group assigned to medical therapy). The high-risk group had a very low FEV₁ and either a very low carbon monoxide diffusing capacity or homogeneous emphysema. All 140 patients had an FEV₁ that was no more than 20 percent of their predicted value. Ninety-four also had evidence of homogeneous emphysema on CT scanning, and 87 also had a carbon monoxide diffusing capacity that was no more than 20 percent of their predicted value. Forty-one patients met all three criteria. The base-line characteristics of these patients were similar in the two treatment groups (Table 1).

Treatment

Sixty-nine of the 70 patients assigned to undergo lung-volume-reduction surgery underwent the procedure and 1 declined the procedure; this patient

TABLE 1. CHARACTERISTICS OF THE HIGH-RISK PATIENTS AT BASE LINE.*

CHARACTERISTIC	SURGERY (N=70)	MEDICAL THERAPY (N=70)
Age at randomization — yr	63.1±6.8	64.2±6.1
Race or ethnic group — no. (%)		
Non-Hispanic white	68 (97)	64 (91)
Non-Hispanic black	2 (3)	5 (7)
Other	0	1 (1)
Sex — no. (%)		
Female	18 (26)	19 (27)
Male	52 (74)	51 (73)
FEV ₁ after bronchodilator use — % of predicted	17.1±2.5	17.3±2.4
TLC after bronchodilator use — % of predicted	132.7±16.7	135.3±19.3
RV after bronchodilator use — % of predicted	267.4±57.1	274.5±55.7
D ₁ CO — % of predicted	20.5±8.9	19.8±7.5
PaO ₂ — mm Hg	60.7±8.6	60.0±9.3
PaCO ₂ — mm Hg	46.8±6.4	47.2±6.0
Perfusion ratio†	0.27±0.15	0.24±0.17
Distribution of emphysema — no. (%)‡		
Heterogeneous	24 (34)	22 (31)
Homogeneous	46 (66)	48 (69)
Maximal workload on bicycle ergometry — W	28.0±17.5	24.2±14.9
Distance walked in 6 min — ft§	1038.2±300.7	993.9±264.1
Average daily score on Quality of Well-Being questionnaire¶	0.58±0.12	0.54±0.12

*High-risk patients were those with a forced expiratory volume in one second (FEV₁) that was no more than 20 percent of their predicted value and either a homogeneous distribution of emphysema on CT scanning or a carbon monoxide diffusing capacity (D₁CO) that was no more than 20 percent of their predicted value. All base-line measurements were obtained after rehabilitation and before randomization, except for carbon monoxide diffusing capacity, which was obtained before rehabilitation and randomization. Plus-minus values are means ±SD. TLC denotes total lung capacity, RV residual volume, PaO₂ partial pressure of arterial oxygen (measured while the patient was breathing ambient air), and PaCO₂ partial pressure of arterial carbon dioxide.

†The perfusion ratio was derived from the radionuclide perfusion scan. Each lung was divided into three zones, with a percentage of the total amount of perfusion assigned to each zone. The ratio was calculated as the sum of the percentages assigned to the upper zones of the left and right lungs divided by the sum of the percentages assigned to the middle and lower zones of the left and right lungs.

‡The distribution of emphysema was based on scores assigned subjectively to each of the three zones in each lung.

§To convert values to meters, divide by 3.28.

¶The Quality of Well-Being scale is a 77-item questionnaire completed by the patient concerning his or her quality of life. The average daily total score ranges from 0 to 1, with higher scores indicating a better quality of life.

was alive four months after randomization. The median time from randomization to surgery was 10 days (range, 3 to 84). Forty-seven patients had a median sternotomy, and 22 had video-assisted thoracoscopy. Four of the 70 patients assigned to receive medical treatment underwent surgery outside the trial. Two of these patients died: one died 22 months after randomization and 1 year after surgery; and the other

TABLE 2. MORTALITY RATES AMONG HIGH-RISK PATIENTS.*

VARIABLE	30-DAY MORTALITY†				OVERALL MORTALITY‡				RISK RATIO (95% CI) FOR SURGERY VS. MEDICAL THERAPY
	SURGERY		MEDICAL THERAPY		SURGERY		MEDICAL THERAPY		
	No. of Patients	No. of Deaths (% [95% CI])	No. of Patients	No. of Deaths	No. of Deaths/Total No. of Patients	Death Rate/Patient-yr	No. of Deaths/Total No. of Patients	Death Rate/Patient-yr	
High-risk group overall	69§	11 (16 [8.2–26.7])	70	0¶	33/70	0.43	10/70	0.11	3.94 (1.9–9.0)
Subgroup FEV ₁ ≤20% of predicted and homogeneous emphysema	45§	8 (18 [8.0–32.1])	48	0	23/46	0.50	5/48	0.08	5.96 (2.2–20.1)
FEV ₁ ≤20% of predicted and D _L CO ≤20% of predicted	44	8 (18 [8.2–32.7])	43	0**	22/44	0.42	8/43	0.14	2.98 (1.3–7.7)

*High-risk patients are those with a forced expiratory volume in one second (FEV₁) that was no more than 20 percent of their predicted value and either a homogeneous distribution of emphysema on CT scanning or a carbon monoxide diffusing capacity (D_LCO) that was no more than 20 percent of their predicted value. A total of 41 patients had all three risk factors (FEV₁ ≤20 percent of the predicted value, a homogeneous distribution of emphysema on CT scanning, and a D_LCO ≤20 percent of the predicted value): 20 in the surgery group and 21 in the medical-therapy group. Five of the 20 patients in the surgery group who had all three factors died within 30 days after surgery. CI denotes confidence interval.

†The 30-day mortality rate was measured from the date of surgery for those in the surgery group and from the date of randomization for those in the medical-therapy group.

‡The analysis was conducted according to the intention to treat. The overall mortality rate was measured from the date of randomization.

§One patient in the high-risk subgroup who was assigned to surgery declined to undergo it and was excluded from this analysis.

¶P<0.001 for the comparison with the surgery group.

||P=0.002 for the comparison with the surgery group.

**P=0.006 for the comparison with the surgery group.

died 6 months after randomization and 21 days after surgery. The other two patients were alive 13 months after surgery.

Mortality and Morbidity

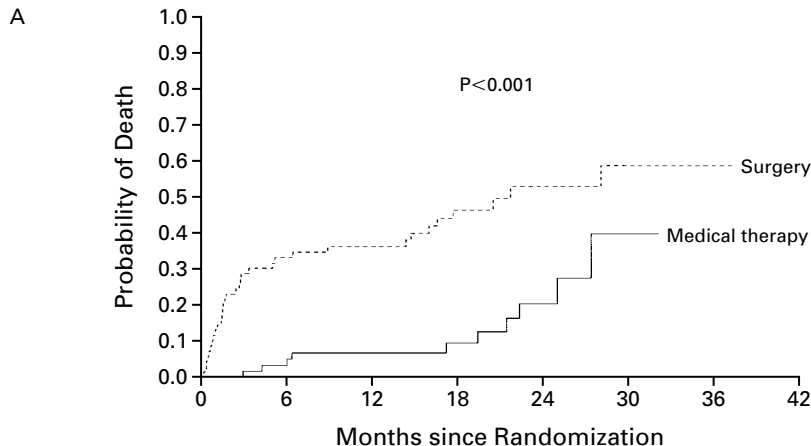
There were no deaths in the medical-therapy group during the first 30 days after randomization. In contrast, the 30-day mortality rate after surgery was 16 percent (95 percent confidence interval, 8.2 to 26.7 percent; P<0.001 for the comparison with the medical group) (Table 2). Patients with all three high-risk characteristics had a 30-day mortality rate of 25 percent (95 percent confidence interval, 8.7 to 49.1 percent) after surgery. The 30-day mortality rate after surgery was similar among patients who had undergone video-assisted thoracoscopy and those who had had a median sternotomy (P>0.99).

The overall mortality rate was 0.43 deaths per person-year among patients assigned to undergo surgery, as compared with 0.11 deaths per person-year among those assigned to receive medical therapy (relative risk of death, 3.9; 95 percent confidence interval, 1.9 to 9.0) (Table 2). The mortality rates during three years of follow-up are shown in Figure 1. The cause of death was most frequently classified as respiratory: 90 percent in the case of patients in the surgery group and 89 percent in the case of patients in the medical-therapy group. Sixty percent of surgical patients and 43 percent of medical patients were receiving mechanical ventilation at the time of death (Table 3). Pneumonia developed in 30 percent of the high-risk patients within 30 days postoperatively.

Although equal numbers of high-risk patients were assigned to the two groups, more patients were

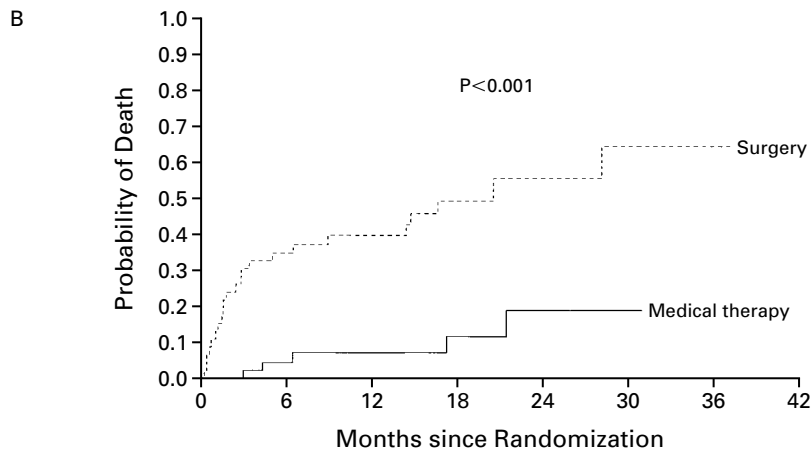
Figure 1 (facing page). Kaplan–Meier Estimates of the Probability of Death among High-Risk Patients, According to Whether They Were Randomly Assigned to Undergo Lung-Volume–Reduction Surgery or Receive Medical Therapy.

This intention-to-treat analysis shows the overall results for the high-risk group (Panel A), the subgroup of patients with an FEV₁ that was no more than 20 percent of their predicted value and a homogeneous distribution of emphysema on CT scanning (Panel B), and the subgroup of patients with an FEV₁ that was no more than 20 percent of their predicted value and a carbon monoxide diffusing capacity that was no more than 20 percent of their predicted value (Panel C). For each analysis the difference between groups was significant (P<0.001, P<0.001, and P=0.005, respectively) by the log-rank test.



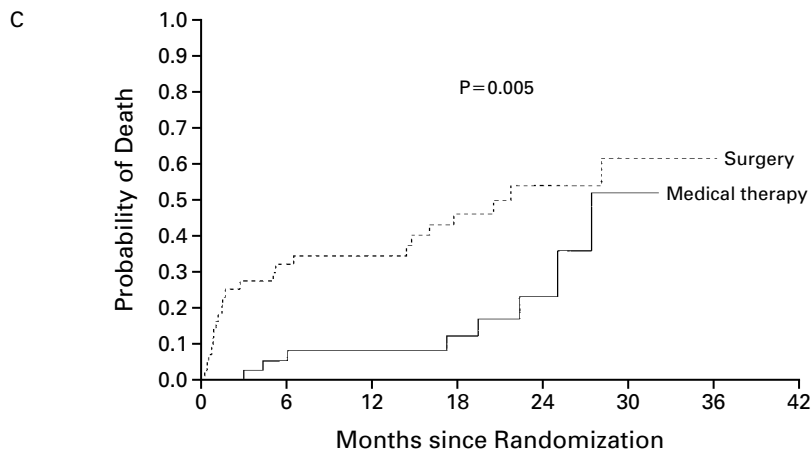
No. AT RISK

Surgery	70	45	37	22	12	6	2
Medical therapy	70	55	44	31	14	2	0



No. AT RISK

Surgery	46	29	21	12	7	3	1
Medical therapy	48	36	28	17	9	1	0



No. AT RISK

Surgery	44	29	25	17	9	4	1
Medical therapy	43	33	26	21	8	2	0

assigned, by chance, to surgery early in the trial, so that 60 such patients were included in the six-month analysis of outcomes, as compared with 51 patients in the medical-therapy group. The distributions of the changes from base line in the scores for functional outcomes six months after enrollment favored neither treatment group (Fig. 2). The surgery group had more deaths, but a few patients in this group had a substantial improvement in functional status. By comparison, more patients in the medical-therapy group were unable to undergo testing because of illness.

When the analysis was confined to survivors who completed the six-month evaluation, the surgery group showed functional improvement in some measures. The mean (\pm SD) change in exercise capacity from base line in the surgery group was an increase of 4.5 ± 13.0 W (measured in 34 patients), as compared with a decrease of 4.4 ± 14.8 W in the medical-therapy group (measured in 23 patients) ($P=0.06$). The surgery group increased the distance walked in six minutes by a mean of 14.9 ± 63.7 m (49 ± 209 ft) (measured in 31 patients), whereas the medical-therapy group had a mean decrease in the distance walked of 21.6 ± 56.7 m (71 ± 186 ft) (measured in 24 patients) ($P=0.03$). Twenty-three percent of the 31 patients in the surgery group increased the distance walked in six minutes by more than 53.9 m (177 ft) — the minimal clinically important difference²³ — as compared with only 4 percent of the 24 patients in the medical-therapy group ($P=0.06$). Patients in the surgery group had a mean increase of 5.5 ± 6.9 percent of the predicted FEV₁ (measured in 34 patients), whereas patients in the medical-therapy group had a mean decrease of 0.4 ± 1.9 percent (measured in 26 patients) ($P<0.001$). Thirty-five percent of the 34 patients in the surgery group had an increase in FEV₁ of at least 200 ml at six months, as compared with none of the 26 patients in the medical-therapy group ($P=0.001$). The score for the Quality of Well-Being questionnaire had decreased by 0.01 unit in both groups at six months ($P=0.94$).

DISCUSSION

This report identifies the characteristics of patients who are at high risk for death after lung-volume-reduction surgery and who also derive little benefit from the procedure. These patients had an FEV₁ that was no more than 20 percent of their predicted value and either homogeneous emphysema or a carbon monoxide diffusing capacity that was no more than 20 percent of their predicted value. Within 30 days after surgery, 16 percent of the patients in this group had died. After six months, only 33 percent of the patients in the surgery group had an improvement in exercise capacity; 23 percent had either no change or a decrease in exercise capacity, 8 percent were unable to complete testing, and 35 percent had died. The health-related quality of life improved in only 28 per-

TABLE 3. CAUSES OF DEATH AND MECHANICAL-VENTILATION STATUS AT THE TIME OF DEATH IN HIGH-RISK PATIENTS.*

VARIABLE	SURGERY	MEDICAL THERAPY
Total no. of deaths	33	10
Cause of death†		
No. of patients in analysis	31	9
Respiratory (%)	90	89
Cardiac (%)	19	11
Gastrointestinal (%)	0	0
Sepsis (%)	10	22
Other (%)	6	0
Mechanical ventilation at time of death‡		
No. of patients in analysis	30	7
Percent of patients	60	43
Mechanical ventilation§		
No. of patients in analysis	18	3
Median no. of days	13	13
Range (days)	1–114	10–20

*High-risk patients were those with a forced expiratory volume in one second that was no more than 20 percent of their predicted value and either a homogeneous distribution of emphysema on CT scanning or a carbon monoxide diffusing capacity that was no more than 20 percent of their predicted value.

†More than one cause of death could be listed for a patient. The cause of death was unknown in the case of two patients in the surgery group and one patient in the medical-therapy group.

‡Mechanical-ventilation status at the time of death was unknown in the case of three patients in each group.

§The analysis included only patients who were receiving mechanical ventilation.

cent of these patients, with 72 percent either dying or having no change or a decrease in the quality of life. The medical-therapy group had a higher percentage of poor functional outcomes but fewer deaths.

Our analysis of functional outcomes took into account deaths and missing data. We used this approach because studies that fail to consider patients who have died or who are unable to complete testing can have biased results.^{12,29} In our study, more surgical patients died, whereas more medical patients were unable to perform functional testing. Patients who did not complete testing but provided no information about why they missed the test were assigned the same functional status as those who were known to be too ill to complete the test. When we accounted for deaths and missing information, there was no significant difference in the distribution of functional outcomes between groups. When we analyzed survivors only, there was a small improvement in FEV₁, exercise capacity, and the distance walked in six minutes in the surgical group.

Our findings have clear importance for the selection of patients for lung-volume-reduction surgery. No single characteristic adequately defines a group of patients for whom the surgery poses a high risk. Sensitivity analyses using different thresholds for FEV₁ and carbon monoxide diffusing capacity and combinations of variables suggest that our criteria for high-

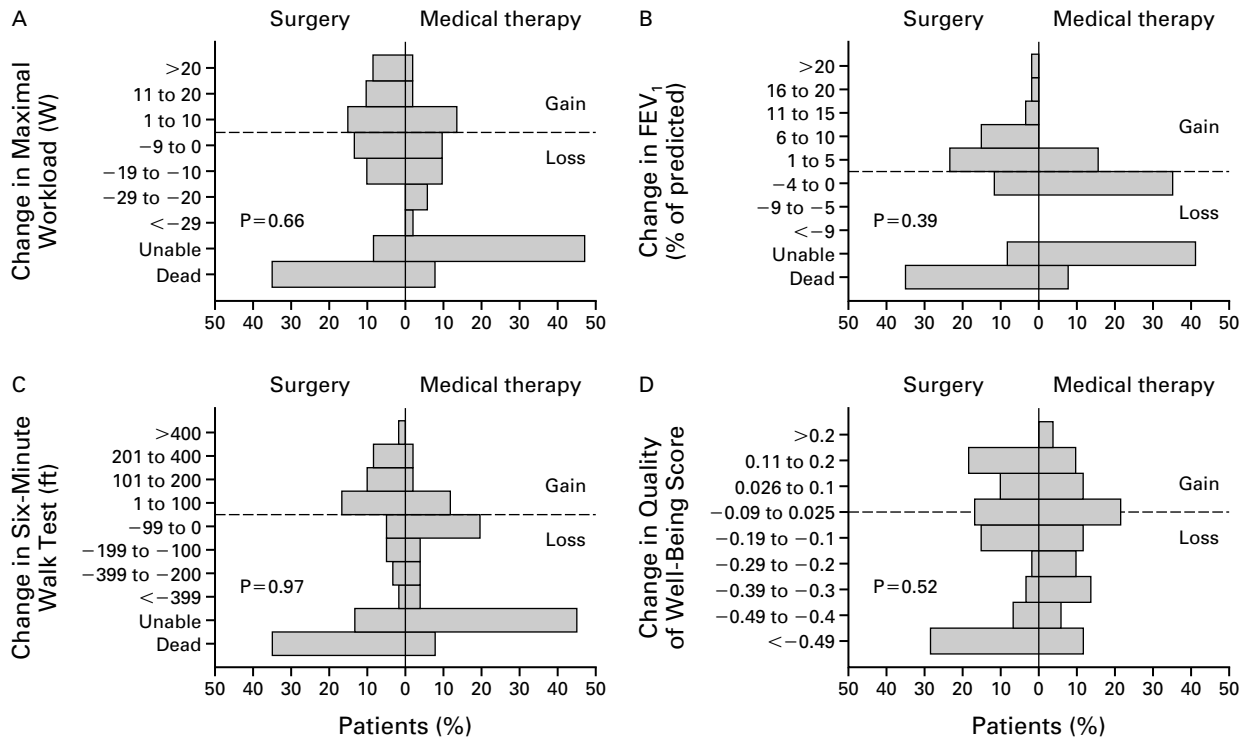


Figure 2. Changes from Base Line to the Six-Month Follow-up Assessment in the Maximal Workload Achieved on Bicycle Ergometry (Panel A), FEV₁ (Panel B), the Distance Covered during the Six-Minute Walk Test (Panel C), and Scores on the Quality of Well-Being Questionnaire (Panel D) among 60 High-Risk Patients Who Were Assigned to Undergo Lung-Volume-Reduction Surgery and 51 Who Were Assigned to Receive Medical Therapy.

The designation “Unable” indicates patients who were too ill to complete the procedure, as well as patients who declined to complete the procedure but who did not explain why they did not complete the procedure. The designation “Dead” indicates patients who died during the first six months of follow-up, even though some of these patients had completed the six-month evaluation before death. Scores on the Quality of Well-Being questionnaire can range from 0 to 1, with higher scores indicating a better quality of life. To convert values from feet to meters, divide by 3.28.

risk patients are nearly optimal. In selecting patients for surgery, we used clinical tests available to community practitioners. The presence of these characteristics should not be considered absolute contraindications to the surgery. In borderline cases, other clinical factors, including the willingness of the patient to accept the risk, should be used to make decisions about the suitability of lung-volume-reduction surgery. Nonetheless, because of the generally unfavorable outcomes, the National Emphysema Treatment Trial no longer enrolls such patients in the clinical trial, and caution should be exercised in performing lung-volume-reduction surgery in such patients.

Our findings are not the result of poor patient selection or a high mortality rate at only a few centers. The high-risk patients were enrolled at all 17 participating clinical centers, and the deaths occurred in the surgery group at 13 of the 17 centers. Although the results of subgroup analyses should be interpreted with caution because of the large number of possible subgroups and the potential for false positive results, such errors are unlikely in this analysis be-

cause of the prespecification of variables of interest and stopping guidelines, the magnitude of the effect, and the plausibility of the findings.

Published information identifying patients at highest risk after lung-volume-reduction surgery is based mainly on small, uncontrolled case series and is contradictory. Some series suggest that a very low FEV₁ is associated with an increased risk of death postoperatively,³⁰ whereas others do not.^{10,31,32} Some case series suggest that a very low carbon monoxide diffusing capacity increases the risk,^{33,34} whereas others have not confirmed this finding.^{32,35-38} A recent trial of lung-volume-reduction surgery involving 48 patients stopped enrolling participants who had a carbon monoxide diffusing capacity that was less than 30 percent of their predicted value or who were unable to walk 150 m (492 ft) on the shuttle-walking test, because 5 of the first 15 patients died (3 in the surgical group and 2 in the medical group).⁴ The cause of the high mortality rate among patients with a low carbon monoxide diffusing capacity may be related to impaired gas exchange. In a rabbit model of

emphysema, a reduction in the diffusing capacity was the physiological factor that limited the amount of lung that could be removed during lung-volume-reduction surgery.³⁹ In patients with a low carbon monoxide diffusing capacity in association with a low FEV₁, resection of lung tissue may restrict the pulmonary vasculature or surface area available for gas exchange enough to cause pulmonary hypertension or worsen hypoxemia, thereby compromising survival.⁴⁰

Although the presence of homogeneous emphysema is associated with less improvement in pulmonary function after lung-volume-reduction surgery than is the presence of heterogeneous emphysema,^{3,32,41-48} it has infrequently been cited as a risk factor for surgical mortality.⁴⁹ In patients with homogeneous disease, lung-volume-reduction surgery involves resection of functional lung tissue. After the removal of functional lung tissue, patients with a very low initial FEV₁ may not derive enough benefit from the surgery to survive postoperative pulmonary complications.

Other factors such as advanced age, hypercapnia, and a low value on the six-minute walk test increase the mortality rate associated with lung-volume-reduction surgery. Although these characteristics are associated with increased death rates, they did not clearly identify patients in our study for whom surgery posed a substantially higher risk than medical treatment.

Our experience in this high-risk group of patients shows that the increased mortality rate persists beyond the 30-day postoperative period. Because ventilatory and circulatory support can maintain life for prolonged periods in patients with severe physiological derangement, it is important to assess the postoperative mortality rate for longer than 30 days and to have as a comparison group a similar group of patients who did not undergo surgery. Patients in both treatment groups had high rates of death from respiratory failure, and many were receiving mechanical ventilation at the time of death.

In conclusion, we have identified a combination of physiological and radiographic characteristics in a group of patients with emphysema that places them at high risk of death after lung-volume-reduction surgery and who also are unlikely to have large improvements in functional status or the quality of life as a result of this procedure. Caution is warranted in the use of lung-volume-reduction surgery in such patients.

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