## Title
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**Authors**
Brenner, M
McKenna, R
Gelb, A
et al.

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# Objective Predictors of Response for Staple Versus Laser Emphysematous Lung Reduction

MATTHEW BRENNER, ROBERT McKENNA, Jr., ARTHUR GELB, KATHRYN OSANN, MARK J. SCHEIN, JOHN PANZERA, HUMPHREY WONG, MICHAEL W. BERNS, and ARCHIE F. WILSON

Departments of Medicine, Pulmonary and Critical Care Division, and Oncology Division, University of California Irvine Medical Center, and Chapman General Hospital, Orange; Lakewood Regional Medical Center, Lakewood; and the Beckman Laser Institute and Medical Clinic, Irvine, California

**Recently described surgical approaches to the treatment of emphysema, including buttressed stapled volume reduction and laser coagulation, are associated with variable clinical outcomes. We examined objective preoperative factors as predictors of response to treatment in patients enrolled in a randomized trial of staple versus laser volume-reduction surgery in order to help define patient selection criteria for these procedures. Seventy-two patients with severe symptomatic emphysema without bullae were entered into the protocol (39 staple, 33 laser). Preoperative objective variables (pulmonary function tests, smoking history, demographics, and graded chest computed tomographic [CT] scans) were evaluated as predictors of response to treatment (defined as a change in $FEV_1$) at 3- to 6-mo follow-up, using linear and multivariate regression analysis. Follow-up pulmonary function was obtained on 90% of the 68 patients surviving at 6 mo. Overall improvement was significant only for staple-treated patients, and improved outcome correlated with greater smoking history and younger age for staple-treated patients. When physiologic variables were analyzed, greater smoking history, lower $DL_{CO}$, and younger age predicted improved outcome for laser-treated patients. Preoperative $FEV_1$ and gas-exchange variables did not predict outcome in staple-treated patients. When CT scan grading was included in multivariate regression analysis, hyperinflation (increased thoracic gas volume) was the primary predictor of response for laser-treated patients. These findings suggest that younger patients with evidence of advanced emphysematous lung disease and hyperinflation are optimal candidates for lung-volume-reduction surgery, particularly by staple-reduction techniques. Additional studies with long-term follow-up, bilateral procedures, and assessment of other outcome measures must be performed to further define operative criteria for lung-volume-reduction surgery for emphysema. Brenner M, McKenna R, Jr., Gelb A, Osann K, Schein MJ, Panzera J, Wong H, Berns MW, Wilson AF. Objective predictors of response for staple versus laser emphysematous lung reduction.**

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Limited effective medical treatment options are available for the more than 1 million persons suffering from emphysema in the United States. In the 1950s, exploratory work described surgical lung-volume-reduction procedures for the treatment of patients with emphysema (1–3). Interest in surgical approaches waned because of marginal acute and long-term success of the initial procedures (1). However, technologic advances and improved operative techniques have led to resurgent interest in the surgical treatment of emphysema in recent years (4–16). Buttressed stapled lung-volume reduction and laser coagulation procedures are currently being investigated for improving respiratory function in severely compromised patients (4–14, 17–19). Cooper and colleagues have reported encouraging preliminary results with bilateral stapled lung-volume-reduction surgery using a median sternotomy approach and staple lines reinforced with bovine pericardium patches to reduce postoperative air-leak complications (5). Thoracoscopic laser treatment of emphysematous patients has shown mixed results in reported series (4, 6, 12–14, 20–24).

Although long-term follow-up data are lacking, volume-reduction surgery appears to be effective in acutely improving objective and subjective pulmonary function in selected patients undergoing the procedure (4, 6, 7, 13, 14, 21–24). Our previous studies had shown that overall response to surgical treatment was greater in staple lung-volume-reduction patients relative to comparable laser-treated patients (19). However, in series reported up to now, the response has been variable, whereas morbidity, mortality, and costs have been significant. Consequently, it is imperative to identify subgroups of patients with optimal response following volume-reduction procedures.

In this study, we evaluated objective pulmonary function tests and graded chest CT scans, using previously published criteria (25), in patients undergoing unilateral and bilateral thoracoscopic staple lung-volume-reduction surgery for emphysematous pulmonary disease. These objective preoperative factors were examined as predictors of response to volume-reduction surgery.

We used changes in $FEV_1$ from preoperative baseline to post-

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Correspondence and requests for reprints should be addressed to Matt Brenner, M.D., Pulmonary and Critical Care Medicine Division, UC Irvine Medical Center, Orange, CA 92668.

operative follow-up values as the major outcome measure. Absolute change in $FEV_1$ following surgery, change in $FEV_1$ % predicted, and % change in $FEV_1$ compared with baseline values were examined to demonstrate the magnitude of changes, as well as relative changes based on level of disease and expected function. Factors that predict response to stapling were assessed for laser and staple surgical volume-reduction procedures.

## METHODS

Patient selection, randomization, and treatment in this protocol have been described previously (19). The protocol was approved by the Institutional Review Board of Chapman General Hospital. Informed consent was obtained from all patients.

### Eligibility

Eligible patients were required to have the following: (*1*) moderate to severe symptomatic emphysema; (*2*) persistence of dyspnea symptoms despite maximal medical therapy; (*3*) hyperexpansion on chest radiography; (*4*) a chest computed tomographic [CT] scan with evidence of severe heterogeneous emphysematous changes in all parts of the lung or more prominent in regional distributions (chest CT scan scores > 50) (25); and (*5*) pulmonary function testing showing severe emphysema. Patients with bullae greater than 3 cm in diameter, age > 75 yr, significant cardiac disease, debilitating disease of other organs, concurrent cancer or lung mass, high-dose steroid dependence (> 20 mg/d prednisone equivalence), bronchiectasis, or ventilator dependency were excluded from entry. All patients had to have discontinued smoking for at least 3 mo to be considered for surgical evaluation.

### Preoperative Evaluation

Full medical history and physical examination were obtained for all patients. Chest radiography (posteroanterior [PA] and lateral), chest CT scan, arterial blood-gas (ABG) measurements, and full pulmonary function testing, including plethysmographic lung volumes, were performed.

### Protocol Design

Patients meeting eligibility criteria and consenting to enrollment were randomly assigned to unilateral laser or buttressed staple volume-reduction surgery. Seventy-two patients were entered into the study. Thirty-three patients were randomized to laser and 39 to staple volume reduction. The randomization was a simple random drawing to laser versus staple surgery. No stratification or grouping was used in the randomization process.

### Postoperative Follow-up

Spirometry was performed on patients surviving 3 to 6 mo (177 ± 76 d mean ± SD) following surgery (19). Twenty six of 30 surviving laser-treated patients returned for follow-up (87%). Thirty six of 38 surviving patients randomized to staple surgery had follow-up spirometry (95%).

### Data Analysis

Univariate and multivariate analyses were conducted with the Systat 5.0 statistical program (Systat, Inc., Evanston, IL). Comparisons between baseline data in the group treated with the staple procedure and the group treated with laser reduction have been previously reported (19). Changes in pulmonary function following the operative procedures were compared for laser- versus staple-treated patients, using a two-tailed Student's *t* test.

Multivariate analyses were designed to predict improvement in lung function following operative procedures, based on baseline data. Three measurements of improvement in lung function were used as outcome variables. These were: (*1*) change in $FEV_1$ (L) from baseline; (*2*) change in $FEV_1$% predicted; and (*3*) percent change in $FEV_1$ compared with baseline, calculated as 100 × ($FEV_1$ follow-up − $FEV_1$ baseline)/$FEV_1$ baseline. Five categories of independent variables likely to affect improvement in lung function were investigated. These included: (*1*) volume variables (thoracic gas volume [TGV], TLC, RV); (*2*) gas-exchange measures ($D_{LCO}$, $P_{O_2}$, $P_{CO_2}$); (*3*) spirometric values (FVC, $FEV_1$, and midexpiratory flow [$FEF_{25-75}$]); (*4*) demographics (height, weight, age); and (*5*) smoking history (pack-years). We attempted to find the "best model" that predicted improvement in lung function for each surgical procedure, using a general linear model of the format:

$$\text{Outcome} = \text{constant} + \text{volume} + \text{spirometric value} + \text{gas exchange measure} + \text{demographics} + \text{smoking} \quad (1)$$

Although the best model is somewhat subjectively defined, we followed steps recommended by Neter and Wasserman (26). First, all univariate associations were examined with the specified outcome variables. Variables selected for inclusion in the multivariate model had to be uncorrelated and associated with the outcome of interest. If more than one variable in a given category met these criteria, each was used in the multivariate model, but not simultaneously, since they were believed to represent a related independent variable. If no variable within a given category reached statistical significance in the univariate analyses, the variable most strongly associated with the outcome variables was chosen for inclusion in the model, in order to control for potential confounding.

Independent variables representing the five different categories were then included in a linear regression model in a stepwise procedure. Variables were stepped into the model according to the amount each contributed to explaining the variance. With this technique, variables that are too highly correlated with a variable already stepped into the model will be screened out. The best model was chosen as that which had the highest $r^2$ value for a given number of variables such that adding in more variables caused only a small increase in the $r^2$.

### Multivariate Analysis with CT Scan Grading

Multivariate analysis was repeated with chest CT scan scoring (25) included in the model to assess the role of extent, severity, and distribution of emphysema as a contributor to outcome. Analysis was performed by stepping CT scan scores and smoking history out of the model.

### Operative Procedures

Operative techniques used for laser treatment and staple volume-reduction procedures have been previously described in detail (19). The patients in our study underwent unilateral video-assisted thoracoscopic surgery under paralyzing (pipecuronium) general anesthesia (isoflurane) given through a left-sided size 39 French double-lumen endotracheal tube (Mallincrodt Anesthesia, St. Louis, MO). After single dependent lung ventilation had been achieved, the contralateral upside deflated lung was examined. The worst distended, destroyed, and emphysematous areas targeted by the preoperative CT lung scan in the upper and midlung fields were excised and linear staple lines were reinforced with bovine pericardium (Peri-Strips; Bio-Vascular, Inc., St. Paul, MN) to minimize air leaks. The mean number of staples fired was nine (range: 4 to 14). It was visually estimated that the excised lung volume was approximately 15 to 20% of each lung. Actual resected lung weighed 30 to 90 g (range). Following lung excision, apical pleural tents and/or talc pleurodesis were not required. Alternatively, if the Nd-YAG contact laser was used, photocoagulation of the worst emphysematous areas was achieved using 10 W of power, and resulted in complete visual contraction of the affected site. The mean joules recorded were 22,598 (range: 14,156 to 29,115).

### Pulmonary Function Testing

Complete pulmonary function testing was performed for all patients within 1 wk prior to surgery, and repeated 3 to 6 mo after discharge from the hospital following laser coagulation surgery in surviving patients. Standard pulmonary function testing included spirometric lung flows, $FEV_1$, FVC, peak inspiratory flow rate (PIF), peak expiratory flow rate (PEFR), maximum voluntary ventilation (MVV), plethysmographic lung volumes (RV, TLC, FRC), airway resistance (Raw), $D_{LCO}$, measured with a Sensormedics Model 2450 (Sensormedics Co, Anaheim, CA), and arterial blood-gas measurements. Specific conductance (SGaw) and TGV were obtained by panting maneuvers at FRC.

## RESULTS

### Randomization and Baseline Characteristics

Thirty-nine patients were randomized to staple treatment and 33 patients to laser treatment. Baseline characteristics of patients are summarized in Table 1. There were no differences in baseline characteristics for laser- versus staple-treated patients.

TABLE 1

BASELINE COMPARISON OF PATIENTS IN THE LASER AND STAPLE PATIENT TREATMENT GROUPS*

| | Laser (Number ± SD) | Staple (Number ± SD) | p Value |
|---|---|---|---|
| Patients Number | 33 | 39 | |
| Male, no. | 26 | 32 | NS |
| Age, yr | 69 ± 6 | 66 ± 8 | NS |
| Height, in | 68 ± 3 | 68 ± 3 | NS |
| Weight, lb | 154 ± 32 | 163 ± 31 | NS |
| $FEV_1$, L | 0.7 ± 0.2 | 0.7 ± 0.2 | NS |
| FVC, L | 2.1 ± 0.7 | 2.1 ± 0.7 | NS |
| RV, L | 5.1 ± 1.1 | 5.4 ± 0.2 | NS |
| TLC, L | 7.6 ± 1.4 | 7.9 ± 1.3 | NS |
| $D_{LCOSB}$, ml/min/mm Hg | 5.4 ± 3.0 | 8.6 ± 19 | NS |
| $Pa_{O_2}$, mm Hg | 65 ± 12 | 66 ± 12 | NS |
| $Pa_{CO_2}$, mm Hg | 43 ± 7 | 44 ± 8 | NS |

* Modified from reference 19.

### Response to Treatment

Overall response in laser- versus staple-treated patients has been previously reported (19). For the outcome variables examined, only staple-treated patients had statistically significant improvement from baseline. There was a significantly greater change in lung function in staple- than in laser-treated patients ($FEV_1$ 0.22 L staple versus 0.09 L laser; $p < 0.02$), and $FEV_1$ percent change from baseline (33% staple versus 13% laser; $p < 0.01$) (19). All of the patients had severe fixed airflow limitation. The FVC was 58 ± 9% predicted (mean SD), and $FEV_1$ was 27 ± 6% predicted (mean SD). There were no immediate deaths in the laser group, but one death (2.5%) in the staple group due to a contralateral tension pneumothorax. At 6 mo follow-up, there were no further deaths in the staple group, but three laser-treated patients had died, although respiratory failure was the cause in only one case.

### Univariate Analysis of Laser-Treated Patients

Results of the univariate analyses are shown in Table 2. Factors predicting improved response to laser treatment (change in $FEV_1$, change in $FEV_1$ % predicted, and % change in $FEV_1$ from baseline) according to univariate analysis include greater preoperative smoking history, lower $D_{LCO}$, and more hyperinflation of lung (TGV or TLC). FRC and RV did not predict response to treatment quite as closely as did TGV. Preoperative $P_{O_2}$, $P_{CO_2}$, or baseline $FEV_1$ did not correlate with response to treatment. There was no association between the total laser energy administration and response. Virtually identical results were seen for predictors of response assessed as percent change in $FEV_1$ compared with baseline (not shown).

### Univariate Analysis of Buttressed Staple-Treated Patients

When physiologic, demographic, and pulmonary function variables were assessed, preoperative smoking history, age, and lung volume (TGV) closely predicted outcome. Again, preoperative $P_{O_2}$, $P_{CO_2}$, or baseline $FEV_1$ did not correlate with response to treatment.

There was a weak association (not statistically significant) of improved response with higher preoperative weight in both staple- and laser-treated patients. Postoperative changes in $FEV_1$ correlated closely with changes in FVC for all patients studied, regardless of treatment subgroup ($n = 35$, $r = 0.7$, $p < 0.0001$ for staple patients; $n = 26$, $r = 0.6$, $p < 0.001$ for laser patients).

### Multivariate Analysis of Laser-Treated Patients

One multivariate model (consisting of the independent variables smoking, TGV, $D_{LCO}$, $FEF_{25-75}$, and age) most closely predicted outcome for all three variables; change in $FEV_1$, change in $FEV_1$ % predicted, and change in $FEV_1$ from baseline, for laser-treated patients (Table 3). Of these independent variables, only smoking history had a consistently significant effect on outcome prediction (Table 3; multiple $r > 0.8$, $p < 0.005$).

### Multivariate Analysis of Buttressed Staple-Treated Patients

For staple-treated patients, a model containing dependent variables similar to those found in laser-treated patients (smoking, TGV, $D_{LCO}$, $FEF_{25-75}$, and age) correlated closely with outcome for all three measures (change in $FEV_1$, change in $FEV_1$% predicted, and change in $FEV_1$ from baseline) (multiple $r > 0.67$, $p < 0.03$). However, only greater smoking history and younger age had a statistically significant influence on outcome as contributors to the regression equation (Table 3).

### CT Scan Grading

CT scan emphysema scores were graded overall and subdivided into upper and lower lung-field scores. Mean overall CT scan score was 62.8 ± 4.1 ($n = 24$) for staple-treated patients versus 5.8 ± 4 ($n = 27$) for laser-treated patients ($p = 0.44$). Preoperative upper-lung-field disease was more severe (64.8 ± 4.4) (in staple-treated patients) than lower lung field disease (48.7 ± 4.4) ($p < 0.01$). Similar differences were seen for upper- versus lower-lung-field disease in the laser-treated patients at 62.2 ± 3.2 for upper-lung-field disease versus 53.3 ± 3.6 for lower-lung-field disease ($p < 0.05$).

CT scan grading of emphysema in upper lung fields correlated with TGV ($r = 0.46$, $p < 0.05$), and showed a weak (not significant) association with smoking history ($r = 0.21$, $p = 0.19$).

When CT scan grades were added to the multivariate regression model, no predictive association was seen. Additionally, smoking history became insignificant as a predictor of outcome

TABLE 2

UNIVARIATE PREDICTORS OF OUTCOME FROM LASER AND STAPLE LUNG-VOLUME-REDUCTION SURGERY

| Change in $FEV_1$ | | | | % Change in $FEV_1$ from Baseline | | | |
|---|---|---|---|---|---|---|---|
| Variable | Correlation | Multiple r | p Value | Variable | Correlation | Multiple r | p Value |
| Laser surgery | | | | | | | |
| Smoking history | + | 0.552 | 0.005 | Smoking history | + | 0.590 | 0.002 |
| $D_{LCO}$ | − | 0.419 | 0.052 | TLC | + | 0.483 | 0.015 |
| TGV | + | 0.414 | 0.049 | TGV | + | 0.474 | 0.022 |
| TLC | + | 0.408 | 0.043 | FRC | + | 0.461 | 0.027 |
| | | | | RV | + | 0.437 | 0.029 |
| | | | | $D_{LCO}$ | − | 0.409 | 0.059 |
| Staple surgery | | | | | | | |
| Smoking history | + | 0.441 | 0.010 | Smoking history | + | 0.360 | 0.043 |
| TLC | + | 0.401 | 0.023 | Age | − | 0.401 | 0.023 |
| | | | | TGV | + | 0.350 | 0.055 |

TABLE 3

MULTIVARIATE PREDICTORS OF OUTCOME FROM LASER AND STAPLE LUNG-VOLUME-REDUCTION SURGERY

| Change in $FEV_1$ | | | | % Change in $FEV_1$ from Baseline | | | | Change in $FEV_1$% Predicted | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Variable | Multiple r | F | p Value | Variable | Multiple r | F | p Value | Variable | Multiple r | F | p Value |
| Laser surgery | | | | | | | | | | | |
| Overall model | 0.668 | 6.59 | 0.021 | Overall model | 0.834 | 6.840 | 0.001 | Overall model | 0.804 | 5.460 | 0.004 |
| | Coefficient | T | | | Coefficient | T | | | Coefficient | T | |
| Smoking | 0.005 | 3.69 | 0.001 | Smoking | 0.728 | 3.870 | 0.001 | Smoking | 0.166 | 3.290 | 0.005 |
| DLCO | −0.036 | −3.30 | 0.005 | DLCO | −4.300 | −2.890 | 0.011 | DLCO | −1.220 | −3.040 | 0.008 |
| Age | −0.01 | −1.57 | 0.136 | Age | −1.340 | 1.570 | 0.130 | Age | −0.239 | −1.040 | 0.313 |
| $FEF_{25-75}$ | 0.39 | 1.05 | 0.308 | $FEF_{25-75}$ | 4.860 | 0.090 | 0.900 | $FEF_{25-75}$ | 9.560 | 0.711 | 0.488 |
| TGV | 0.024 | −1.60 | 0.565 | TGV | 6.410 | 1.150 | 0.270 | TGV | 1.470 | 1.000 | 0.337 |
| Staple surgery | | | | | | | | | | | |
| | Multiple r | F | | | Multiple r | F | | | Multiple r | F | |
| Overall model | 0.668 | 3.38 | 0.020 | Overall model | 0.743 | 5.160 | 0.003 | Overall model | 0.670 | 3.250 | 0.026 |
| | Coefficient | T | | | Coefficient | T | | | Coefficient | T | |
| Smoking history | 0.004 | 3.18 | 0.005 | Smoking history | 0.568 | 3.380 | 0.003 | Smoking history | 0.139 | 3.360 | 0.003 |
| Age | −0.007 | −1.70 | 0.097 | Age | −1.300 | −2.190 | 0.039 | Age | −0.206 | −1.410 | 0.173 |
| TGV | 0.04 | 1.40 | 0.175 | TGV | 7.580 | 1.900 | 0.070 | TGV | 0.997 | 1.020 | 0.319 |
| DLCO | 0.009 | 0.72 | 0.484 | DLCO | 2.210 | 1.190 | 0.246 | DLCO | 0.270 | 0.596 | 0.558 |
| $FEF_{25-75}$ | 0.361 | 1.09 | 0.287 | $FEF_{25-75}$ | −11.500 | 0.250 | 0.805 | $FEF_{25-75}$ | 8.130 | 0.709 | 0.487 |

for either staple or laser surgery when CT scan scores were added to the model. TGV became the only significant predictor of outcome for laser-treated patients when CT scan scoring was added to the regression model (Table 4).

## DISCUSSION

Bovine pericardium-buttressed stapling and thoracoscopic laser methods have been described for surgical treatment of pulmonary emphysema (4–13, 19). Limited information is available about clinical response to these treatment techniques or for defining optimal patient selection characteristics (4, 7–11, 13, 15, 16, 21, 22).

We undertook a randomized, prospective clinical trial comparing unilateral thoracoscopic reinforced stapling with laser treatment in a defined subgroup of emphysema patients with severe symptomatic emphysema. Entry criteria were restricted to patients with diffuse emphysema (and without large bullae) to see whether improvement in function could occur in this group of patients, who have generally been considered unlikely to benefit from surgical intervention. As recently reported (19), only patients who were randomized to unilateral staple volume-reduction surgery had a significant improvement in $FEV_1$ and FVC at follow-up 3 to 6 mo post operatively. Overall, patients treated with unilateral laser procedures alone did not have statistically objective spirometric improvement in that study (19).

In the current study, we extended the previous analysis in order to determine which subgroups of patients with diffuse emphysema respond best to surgery based on objective preoperative criteria. The goals of this analysis focus on: (*1*) determining characteristics associated with optimal response to treatment that may be useful in developing patient selection criteria; (*2*) de-

TABLE 4

EFFECT OF CT SCAN SCORE ON MULTIVARIATE PREDICTORS OF OUTCOME FROM LASER AND STAPLE LUNG-VOLUME-REDUCTION SURGERY

| Change in $FEV_1$ | | | | % Change in $FEV_1$ from Baseline | | | | Change in $FEV_1$% Predicted | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Variable | Multiple r | F | p Value | Variable | Multiple r | F | p Value | Variable | Multiple r | F | p Value |
| Laser surgery | | | | | | | | | | | |
| Overall model | 0.636 | 1.90 | 0.150 | Overall model | 0.611 | 1.660 | 0.200 | Overall model | 0.716 | 2.950 | 0.050 |
| | Coefficient | T | | | Coefficient | T | | | Coefficient | T | |
| TGV | 0.0905 | 2.13 | 0.050 | TGV | 13.988 | 1.917 | 0.076 | TGV | 3.145 | 2.159 | 0.049 |
| DLCO | −0.0098 | −0.82 | 0.425 | DLCO | −1.314 | −0.642 | 0.531 | DLCO | −0.404 | −0.998 | 0.335 |
| $FEF_{25-75}$ | 0.1386 | 0.37 | 0.718 | $FEF_{25-75}$ | −12.494 | −0.194 | 0.849 | $FEF_{25-75}$ | −1.227 | −0.095 | 0.926 |
| Age | −0.0016 | −0.24 | 0.817 | Age | −0.553 | −0.477 | 0.641 | Age | 0.063 | 0.277 | 0.786 |
| CT scan score | 0.0004 | 0.26 | 0.797 | CT scan score | 0.011 | 0.041 | 0.968 | CT scan score | 0.098 | 1.761 | 0.970 |
| Staple surgery | | | | | | | | | | | |
| | Multiple r | F | | | Multiple r | F | | | Multiple r | F | |
| Overall model | 0.501 | 0.80 | 0.570 | Overall model | 0.621 | 1.500 | 0.260 | Overall model | 0.431 | 0.550 | 0.730 |
| | Coefficient | T | | | Coefficient | T | | | Coefficient | T | |
| TGV | 0.056 | 0.82 | 0.429 | TGV | 7.091 | 0.755 | 0.465 | TGV | 1.086 | 0.444 | 0.665 |
| DLCO | −0.0197 | −1.06 | 0.310 | DLCO | −1.242 | −0.487 | 0.635 | DLCO | −0.695 | −1.049 | 0.315 |
| $FEF_{25-25}$ | −0.0527 | −0.09 | 0.926 | $FEF_{25-25}$ | 85.602 | −1.117 | 0.286 | $FEF_{25-25}$ | −9.294 | −0.466 | 0.650 |
| Age | −0.0068 | −0.93 | 0.372 | Age | −0.887 | −0.884 | 0.394 | Age | −0.112 | −0.428 | 0.676 |
| CT scan score | −0.002 | −0.73 | 0.479 | CT scan score | −0.210 | −0.556 | 0.589 | CT scan score | −0.054 | −0.546 | 0.595 |

termining whether there are subgroups of patients who might benefit from laser procedures even though benefit was not significant in the overall group; and (*3*) identifying preoperative variables that may be helpful in comparing results from other published series (e.g., assessing the influence of patient selection when evaluating results of particular operative techniques).

The previous literature on standard surgical bullectomy, reports of laser and staple volume reduction, and our own experience have suggested that a number of characteristics may be important in predicting objective postoperative outcome. Certain positive prognostic factors are repeatedly identified from these studies, including younger age, preoperative hyperinflation, inhomogeneous upper-lobe-predominant disease, and absence of bronchitis or inflammatory airway disease. We focused the present study on some of these and other objective predictors of response that could be easily obtained preoperatively.

For evaluations done with univariate analysis, the greatest improvements were found in patients with severe preoperative hyperinflation. Younger age was also associated with greater improvement.

With multivariate linear analysis, consistent models were found to predict outcome, regardless of which specific $FEV_1$ measurement outcome variable was selected (change in $FEV_1$, $FEV_1$% predicted, or percent change from baseline). When only physiologic, demographic, and pulmonary function variables were analyzed in the regression model (i.e., without radiographic information), patients with the greatest cigarette exposure had the greatest response in all groups. Aside from radiologic predictors, smoking history was clearly the variable that demonstrated the strongest correlation with response in both univariate and multivariate analysis for every subgroup. We speculated that this might be an indirect reflection of the degree of underlying emphysema, particularly associated with inhomogeneous upper-lobe disease. However, since patients with evidence of reversible airway disease, bronchitis, or nonemphysematous causes of dyspnea were excluded from study entry, the applicability of smoking history to prediction of eligibility cannot be generalized to patients who have not had the other preoperative pulmonary evaluations used in our study (pulmonary function tests, chest radiographs, and CT scans).

CT grading of degrees of emphysema did not appear to increase the accuracy of outcome predictions when added to the physiologic variables in our regression model. This was probably because of limitations of the CT emphysema scoring method used for this application. CT scan readings correlated moderately closely with outcome as a univariate predictor. The CT scans were graded at only a limited number of levels, and inhomogeneity of disease was present, with some areas of high and low scores in most cases. In inhomogeneous disease, average values for upper-lobe and lower-lobe disease may not give an accurate overall representation, which may be optimal for response. Coexisting airway disease or other factors may reduce the response to surgery in what otherwise appears to be emphysematous lung, possibly affecting correlation with response. Location of disease or any other variables that also affect outcome will reduce the predictive value of an overall average CT scan scoring system. Additionally, CT scans from outside referral sites were of variable quality, limiting the comparability of readings in some cases. Most importantly, the outcome variable itself ($FEV_1$) is an imperfect measure; therefore, correlation with CT scan scores would be expected to have limitations. Thus, accurate radiologic prediction of outcome will require more sophisticated radiologic grading methods.

Smoking history loosely correlated with CT scan score. Neither variable (smoking history or CT grade) significantly predicted outcome when both were included in the model, leaving lung volume predominant as the single factor predicting improvement in $FEV_1$. When smoking history was stepped out of the regression model, CT scan score correlated with outcome more strongly than when smoking history was included.

$P_{CO_2}$, $P_{O_2}$, or $FEV_1$ did not predict acute outcome in this series. Patients with lower $P_{O_2}$ and $FEV_1$ values had no overall difference in $FEV_1$ improvement from patients with higher baseline presentations. The lack of correlation between $P_{CO_2}$ and response to treatment was surprising, since $CO_2$ retention is widely believed to be a relative contraindication to volume-reduction surgery as well as traditional bullectomy. In this series, significant preoperative $CO_2$ retention was an exclusion criterion. Thus, the range of preoperative $P_{CO_2}$ values in patients admitted into the protocol was narrow, and correlations may have been missed, particularly in potentially higher risk $CO_2$-retaining patients.

A low $D_{LCO}$ has been considered predictive of poor response to standard surgical bullectomy because it is generally indicative of more severe emphysema in remaining tissue surrounding the bullae. During bullectomy, adequate function in surrounding lung tissue predicted improved response to treatment. In contrast, in our series, low $D_{LCO}$ correlated with better response to laser treatment. Patients with bullous lung disease were excluded from the study. Therefore, the physiologic mechanisms of response to volume reduction in our patients are likely to have differed from those of bullectomy patients. With lung-volume-reduction surgery, the most important issue may be the presence of regions of emphysema sufficiently advanced to allow improvement with removal and volume reduction (probably from increased elastic recoil following the removal of severely emphysematous regions). Lower $D_{LCO}$ may be indicative of the presence of severe emphysema, with associated increased potential benefit from removal of diseased tissue. In contrast, airway disease and asthma would be expected to present with relatively preserved $D_{LCO}$, in comparison with $FEV_1$ reduction, and would not be expected to respond as well to volume-reduction surgery.

Our study was limited by the short duration of follow-up. Factors associated with optimal long-term benefit may be distinct from those associated with 3- to 6-mo benefit. The procedures used in the study were unilateral, and responses may be different for bilateral procedures. Only a single objective spirometric endpoint of response was analyzed ($FEV_1$). Different preoperative presentations could be associated with optimal response if other outcome variables were assessed. Additionally, preoperative selection criteria used for patients in the study defined a relatively homogeneous operative population. Thus, parameters for some important predictive variables may have been so narrowly selected that their effects could not be detected in the regression models. Interactions among the analysis variables and covariance may have altered the relative magnitude of the predictive value for some variables.

No single measurement clearly describes pulmonary function or accounts for dyspnea symptoms or exercise ability (7, 27–30). The use of $FEV_1$ as the primary outcome variable has significant limitations: Improvement in $FEV_1$ correlates poorly with subjective changes in dyspnea in most published studies; exercise function may more closely model requirements for the performance of daily activities. $FEV_1$ correlates only indirectly with changes in elastic recoil, which we hypothesize cause improvement in function. Nonetheless, use of $FEV_1$ as the primary endpoint for outcome assessment appears reasonable despite these limitations. $FEV_1$ is objective. Studies using subjective endpoints have been heavily influenced by the placebo effect in this area of investigation. There has been considerable criticism of many published reports of subjective improvement following surgical procedures, in which objective measures of improved outcome are lacking. $FEV_1$ is reasonably reproducible and relatively independent of patient effort in severely emphysematous patients. Additionally, $FEV_1$ is not influenced by training effects or deconditioning, which complicate exercise measurements. Also, $FEV_1$ has been reported in most series, enabling some degree of comparison across techniques. Furthermore, the suspected mechanisms of improvement (increased elastic recoil and airway support) would be expected to be manifested by improvements in $FEV_1$.

The findings in the present study are consistent with expectations from the prior literature. A number of recently published reports have described the use of different techniques that put these findings in clearer perspective. Little and colleagues reported on patients with a mix of bullous and nonbullous emphysema treated with unilateral free-beam Nd:YAG laser thoracoscopic procedures who showed an 18% overall improvement in $FEV_1$ from baseline (23). Wakabayashi reported $FEV_1$ follow-up results on 224 of 500 patients who underwent unilateral or bilateral contact-tip Nd:YAG laser volume-reduction surgery (some with excision and stapling as well) and mixed presentations (14). Overall, 33% improvement was seen in $FEV_1$ from baseline. Eugene and associates reported a 34% improvement in patients with mixed presentations undergoing unilateral combined staple and laser thoracoscopic reduction procedures (24). Cooper and coworkers reported an 82% improvement from baseline in diffusely emphysematous patients undergoing bilateral staple volume reduction surgery via median sternotomy.

Thus, in reported series of patients with predominantly nonbullous emphysema, it appears that unilateral laser procedures result in only small improvements in $FEV_1$ (approximately 13 to 30% from baseline). In series that include some patients with large bullae, the average improvements appear to be somewhat greater (4). Unilateral staple procedures in emphysematous patients appear to result in significantly greater improvements (30 to 40%) from baseline (19), with mixed staple-and-laser procedures producing similar results to those of stapling alone (24). Bilateral staple volume-reduction surgeries appear to result in substantially greater improvements in $FEV_1$ (50 to 82%) from baseline.

In summary, we found that objective preoperative presentation may assist in predicting response to lung-volume-reduction surgery to some degree. The finding that preoperative objective physiologic factors did not show a stronger predictive relationship to outcome probably reflects the relatively uniform nature of the selected patient population in our study and our limited ability to quantitate radiographic presentation accurately enough for stratification in multivariate analysis. Results of this study, in the context of other recently reported series, suggest that unilateral staple procedures provide greater improvement than current laser reduction techniques, and that younger patients with a greater smoking history and hyperinflation have optimal responses to staple volume reduction. Lower $FEV_1$ does not appear to be a contraindication to surgery. Additional studies with long-term follow-up, bilateral procedures, and assessment of other outcome measures must be performed to further define operative criteria for lung-volume-reduction surgery for emphysema.

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