RELATION BETWEEN PREOPERATIVE INSPIRATORY LUNG RESISTANCE AND THE OUTCOME OF LUNG-VOLUME–REDUCTION SURGERY FOR EMPHYSEMA

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ABSTRACT

Background Surgery to reduce lung volume has recently been reintroduced to alleviate dyspnea and improve exercise tolerance in selected patients with emphysema. A reliable means of identifying patients who are likely to benefit from this surgery is needed.

Methods We measured lung resistance during inspiration, static recoil pressure at total lung capacity, static lung compliance, expiratory flow rates, and lung volumes in 29 patients with chronic obstructive lung disease before lung-volume–reduction surgery. The changes in the forced expiratory volume in one second (FEV_1) six months after surgery were related to the preoperatively determined physiologic measures. A response to surgery was defined as an increase in the FEV_1 of at least 0.2 liter and of at least 12 percent above base-line values.

Results Of the 29 patients, 23 had some improvement in FEV_1 including 15 who met the criteria for a response to surgery. Among the variables considered, only preoperative lung resistance during inspiration predicted changes in expiratory flow rates after surgery. Inspiratory lung resistance correlated significantly and inversely with improvement in FEV_1 after surgery ($r=-0.63$, $P<0.001$). A preoperative criterion of an inspiratory resistance of 10 cm of water per liter per second had a sensitivity of 88 percent (14 of 16 patients) and a specificity of 92 percent (12 of 13 patients) in identifying patients who were likely to have a response to surgery.

Conclusions Preoperative lung resistance during inspiration appears to be a useful measure for selecting patients with emphysema for lung-volume–reduction surgery. (N Engl J Med 1998;338:1181-5.)

CHRONIC obstructive pulmonary disease, which is estimated to affect 14 million persons in the United States, is "characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema."[1] In chronic bronchitis, airflow is obstructed by inflammation and edema of the airway, hypersecretion of mucus, and constriction of bronchial smooth muscle. In emphysema, airflow is obstructed by the loss of elastic recoil and diminished airway tethering as a result of parenchymal destruction.

In recent years, surgery to reduce lung volume has been reintroduced to alleviate dyspnea and improve exercise tolerance in selected patients with emphysema.[2] This operation, first suggested by Brantigan in the late 1950s, removes poorly functioning peripheral areas of emphysematous lung.[3] In most series, patients chosen for surgery have a heterogeneous distribution of parenchymal destruction, preferably centered in the upper lobes. Such a distribution is present only in about 25 percent of patients with moderate-to-severe disease.[4] Early results have been promising, but not all patients benefit from surgery.[5-9]

In this report, physiologic, rather than anatomical, variables were used to predict the benefit of surgery. If, as proposed by Brantigan, surgery to reduce lung volume improves lung function by increasing elastic recoil and airway tethering, then the most important determinant of responsiveness is the extent to which loss of recoil and airway tethering is responsible for the obstruction of airflow.[3] Patients with obstruction due to intrinsic airway disease are not thought to benefit from this type of surgery. The lung-function tests commonly used to evaluate candidates for lung-volume–reduction surgery do not determine the mechanisms responsible for airflow obstruction in a given patient.

We reasoned that lung resistance measured during inspiration would be a useful screening criterion for evaluating the aptness of patients for surgical therapy. Patients with markedly elevated inspiratory resistance are likely to have predominantly airway disease. We predicted that in such patients expiratory flow would not improve in response to lung-volume–reduction surgery. Conversely, patients with less-elevated inspiratory resistance are likely to have obstruction as a result of dynamic airway collapse due to loss of airway tethering by lung parenchyma. We predicted that in such patients expiratory flow would improve as a result of surgery to reduce lung volume.

METHODS

Patients

Twenty-nine patients, 16 men and 13 women, with severe end-stage chronic obstructive pulmonary disease thought to be predominantly due to emphysema agreed to participate in the study, which was conducted between October 1994 and July 1997. All

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TABLE 1. PREOPERATIVE CHARACTERISTICS OF THE 29 PATIENTS.*

CHARACTERISTIC	VALUE
Mean age (yr)	59.6±8.6
Sex (M/F)	16/13
Smoking history (pack-yr)	
Mean	69±30
Range	25–125
Oxygen requirement (liters/min)†	
Mean	2.4±0.7
Range	0–5
Oral glucocorticoids (no. of patients)	9
Karnofsky score‡	
Mean	71±6
Range	60–80
Forced expiratory volume in one second	
Liters	0.64±0.21
% of predicted value	21±7
Forced vital capacity	
Liters	2.09±0.72
% of predicted value	56±15
Total lung capacity§	
Liters	6.38±1.82
% of predicted value	104±21
Residual volume§	
Liters	3.84±1.53
% of predicted value	177±59
Carbon monoxide diffusing capacity¶	
Milliliters/min/mm Hg	8.3±2.8
% of predicted value	33±12
Static recoil pressure at total lung capacity (cm of water)‖	9.6±2.7
Static lung compliance (liters/cm of water)‖	0.25±0.18
Lung resistance (cm of water/liter/sec)	9.5±4.2

*Plus–minus values are means ±SD. In four control subjects the respective values for static recoil pressure at total lung capacity, static lung compliance, and lung resistance were 29.5±4.4 cm of water, 0.09±0.04 liter per centimeter of water, and 1.0±0.2 cm of water per liter per second.

†Twenty-two patients required oxygen, and seven patients were oxygen-independent.

‡Data were available on 28 patients. A score of 100 indicates completely normal function, a score of 80 a moderate reduction in function, and a score of 60 a severe reduction in function.

§Data were available on 25 patients.

¶Data were available on 21 patients.

‖Data were available on 27 patients.

patients provided written informed consent under a protocol approved by the hospital's institutional review board. All patients completed the study. The base-line characteristics of the patients are summarized in Table 1. The details of the surgical procedure, but not the preoperative physiologic studies, have previously been described for 11 of these patients.[10]

The patients ranged in age from 42 to 75 years (mean [±SD], 59.6±8.6), and all were between 80 percent and 130 percent of their ideal body weight. None had a history of childhood asthma or atopy, a history suggestive of bronchiectasis, or a history of inhalation injury or exposure to drugs that might cause bronchiolitis. All patients had been cigarette smokers, and all reported abstinence from cigarettes for at least four months before being evaluated for surgery. All but 3 patients were receiving more than one type of bronchodilator therapy: 26 received combined therapy with a selective β_2-agonist and anticholinergic agent, 21 received inhaled glucocorticoids, and 9 received low-dose oral glucocorticoids (≤10 mg of prednisone per day). Nineteen patients were receiving continuous oxygen, three used oxygen during physical exertion and sleep, and seven did not use oxygen.

Criteria for Surgery

Indications for surgery included severe dyspnea and airflow obstruction as assessed by spirometry, with evidence of hyperinflated lungs and flattened diaphragms on chest radiography and the presence of emphysema on computed tomographic (CT) scanning of the chest. All patients were required to participate in a six-week program of pulmonary rehabilitation. Relative contraindications to surgery were the presence of severe concurrent illnesses (such as myocardial ischemia), pulmonary-artery hypertension (a pulmonary-artery systolic blood pressure of more than 45 mm Hg or a mean pressure of more than 35 mm Hg), or pleural scarring; the use of excessive doses of glucocorticoids (>10 mg of prednisone per day); and the failure to complete the preoperative rehabilitation program. Evaluation included spirometry, exercise oximetry, chest radiography, chest CT scanning, quantitative ventilation–perfusion lung scanning, and stress dobutamine echocardiography, in addition to a complete history taking and physical examination.[10,11] CT evidence of a heterogeneous pattern of parenchymal destruction or of destruction largely confined to the upper lobes was not included in the selection criteria.

Assessment of Functional Capacity

All patients reported substantial functional limitation preoperatively. The Karnofsky scale was used to assess functional status at the time of initial presentation for surgical evaluation.

Physiologic Studies

Pulmonary-function tests were performed on a spirometer (P.K. Morgan) according to standard American Thoracic Society guidelines.[12] Lung volumes were determined by calculating helium dilution with a seven-minute period of equilibration. Diffusion capacity was determined by the single-breath carbon monoxide method.[13]

The static recoil pressure of the lungs at total lung capacity and pressure–volume curves of the lung during deflation were determined in all patients by measuring transpulmonary pressures with an esophageal balloon and a mouth pressure port connected to a differential transducer. Pressures during deflation were determined by interrupting expiratory flow for several seconds to allow measurement of static pressure. Correct positioning of the balloon was confirmed by the demonstration of consistently negative fluctuations in pressure during inspiration and the absence of a change in transpulmonary pressure during airway occlusion. Flow was measured with a pneumotachometer (model 1, Fleisch). Analogue pressure and flow signals were digitized and processed with a microcomputer. Volume was determined by digital integration of the flow signal.

Static pressure–volume curves during deflation were fitted to the exponential equation of Salazar and Knowles[14]:

$$P_{st} = -1/K \ln [(V_{max} - V)/(V_{max} - V_{min})],$$

where P_{st} and V are the static expiratory recoil pressures and lung volumes, respectively, and maximal volume (V_{max}), minimal volume (V_{min}), and the shape factor (K) were determined from curve fitting with a least-squares minimization.[14] This equation was used to generate an expiratory pressure–volume curve from which static lung compliance (calculated as the slope between total lung capacity and total lung capacity − 0.5 liter) was determined.

Lung resistance (R_L) and dynamic elastance (E_{dyn}) were calculated during spontaneous breathing by measuring changes in transpulmonary pressure (ΔP_L), airflow at the mouth ($\dot{V}$), and tidal volume as the integral of flow. Resistance and elastance were determined by multivariate regression with a simple linear form of the equation of motion[15]:

$$\Delta P_L = R_L \dot{V} + E_{dyn} \int \dot{V} dt.$$

Resistance values represent the average results from several breaths. The quality of fit of the measured data to the equation of motion was assessed by examining the statistical variable r^2, which describes the ability of the linear equation to explain the observed variance in measured results. In a subgroup of 11 patients inspiratory and expiratory resistance values were calculated separately. Expiratory resistance was much greater than inspiratory resistance, and the quality of the fit of the data to the linear model was poor, as has been previously described.[16] Thus, only resistance during inspiration was considered. Analysis of the goodness of fit between the data measured during inspiration and the linear model confirmed the goodness of fit among patients in the cohort, with r^2 values of ≥ 0.8 for 27 of the 29 patients.

Surgical Technique

Lung volume was reduced by sequential unilateral thoracoscopic plication in 25 patients and bilateral plication in 4 patients.[10] Quantitative ventilation–perfusion scanning was used to identify the lung with the least function, and this lung was operated on first. Patients who underwent unilateral plication were allowed to recover fully from surgery before the volume of the contralateral lung was reduced in a similar fashion eight weeks to eight months later. The mean length of hospitalization was 10.0±8.5 days (median, 7).

Statistical Analysis

Data are summarized as means ±SD. Comparisons between preoperative and postoperative values were made with Student's paired t-test. Comparisons between patients with responses and those without responses were made with Student's unpaired t-test. Univariate and multivariate linear regression analyses were used to assess continuous relations between variables.[17] A P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Preoperative Findings

The preoperative functional capacity, results of spirometry, and lung-volume measurements in the 29 patients are summarized in Table 1. Functional capacity, as assessed by the Karnofsky scale, was consistent with the presence of moderate-to-severe limitation of activity. Spirometry demonstrated severe obstruction; in all patients the forced expiratory volume in one second (FEV_1) was less than 37 percent of the predicted value. Lung volume was measured on the basis of helium dilution in 25 patients and showed that total lung capacity was only minimally elevated, whereas residual volume was markedly elevated. Diffusing capacity corrected for the hemoglobin concentration was reduced in all 21 patients in whom it was assessed.

Values for lung resistance and static lung compliance in the patients were compared with measurements made in four control subjects without obstructive lung disease. Static lung compliance was higher in the patients than in the control subjects (0.25±0.18 vs. 0.09±0.04 liter per centimeter of water), and static recoil pressure at total lung capacity was lower (9.6±2.7 vs. 29.5±4.4 cm of water). During spontaneous breathing (mean frequency, 17.5±4.0 breaths per minute; range, 10 to 24), inspiratory resistance was nearly nine times as high in patients with emphysema as in control subjects (9.5±4.2 vs. 1.0±0.2 cm of water per liter per second). The patients' inspiratory-resistance values were similar to those previously reported in patients with chronic obstructive lung disease.[16]

Postoperative Findings

After lung-volume–reduction surgery, forced expiratory flow significantly increased in the group as a whole. Six months after surgery, FEV_1 had improved 33 percent to 0.85±0.39 liter, a change of 0.21±0.36 liter (P<0.001), and forced vital capacity had increased by 18 percent to 2.46±0.96 liters, a change of 0.37±0.50 liter (P<0.001). The improvement in these values was not uniform among patients (Fig. 1). Twenty-three patients had some improvement in FEV_1 after surgery, whereas six had a decline. Of the 23 patients with a postoperative increase in FEV_1, 15 had an increase of at least 0.2 liter and of at least 12 percent, as compared with baseline values, thus satisfying American Thoracic Society criteria indicating a decrease in airflow obstruction.[12] Data on these 15 patients were compared with data on the 14 patients who did not meet the criteria for a decrease in obstruction. Preoperative values for FEV_1, forced vital capacity, total lung capacity, and residual volume (the last two measured by helium dilution) were similar between the groups. In contrast, among the patients who responded to surgery, preoperative values for static recoil pressure

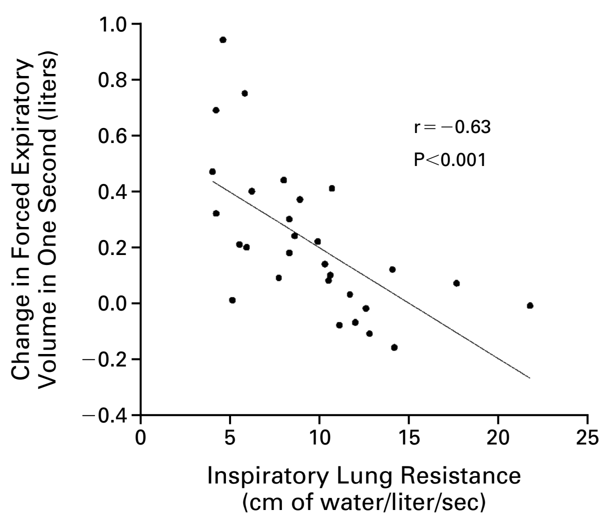

Figure 1. Correlation between Preoperative Inspiratory Lung Resistance and the Change in Forced Expiratory Volume in One Second Six Months Postoperatively.

Lung resistance was measured during spontaneous breathing. There was a significant inverse correlation (r = −0.63, P<0.001) between the variables.

at total lung capacity (8.1±3.1 vs. 10.6±2.3 cm of water, P=0.03) and inspiratory lung resistance during spontaneous breathing (6.9±2.2 vs. 12.3±4.0 cm of water per liter per second, P<0.001) were significantly lower, and static lung compliance was greater (0.32±0.22 vs. 0.19±0.08 liter per centimeter of water, P=0.07). Values in both groups differed significantly from values in control subjects (data not shown).

Predictive Characteristics

We used univariate and multivariate linear regression analysis to assess the ability of nine variables measured preoperatively to predict the response to lung-volume–reduction surgery. The postoperative change in FEV_1 was correlated with preoperative FEV_1 (calculated as the percentage of the predicted value), static recoil pressure at total lung capacity, static lung compliance, the shape factor K (calculated according to the equation of Salazar and Knowles[14]), residual volume, lung resistance during inspiration, age, sex, and smoking history. Univariate analysis showed that only preoperative inspiratory lung resistance was significantly correlated with the postoperative change in FEV_1 (Fig. 1). Multivariate regression analysis confirmed that only preoperative inspiratory lung resistance was correlated significantly with an improvement in FEV_1. Further statistical analysis demonstrated that the relation between inspiratory lung resistance and the postoperative change in FEV_1 did not appear to be dependent on the finding of very favorable results in only a few patients, despite the relatively small size of the cohort (data not shown).

A preoperative criterion of an inspiratory resistance of 10 cm of water per liter per second had a sensitivity of 88 percent and a specificity of 92 percent in identifying patients who were likely to have a favorable response to lung-volume–reduction surgery. Fourteen of 16 patients with an inspiratory resistance of less than 10 cm of water per liter per second preoperatively had an increase in FEV_1 of at least 0.2 liter or of at least 12 percent above baseline values, whereas 12 of 13 patients with an inspiratory resistance of more than 10 cm of water per liter per second did not.

DISCUSSION

Preoperative lung resistance during inspiration in this group of 29 patients with severe airflow obstruction was predictive of the change in expiratory flow rates after surgery to reduce lung volume. Measurements of lung resistance in such patients can be problematic. Mead and colleagues have demonstrated that in patients with chronic obstructive pulmonary disease, in contrast to healthy control subjects, the relation between pressure and flow during exhalation is not linear, which precludes the assignment of a single value for lung resistance.[16] They found that during inspiration the relation between pressure and flow is approximately linear in both patients and control subjects. Our data are consistent with these prior observations, with inspiratory pressure and flow measurements demonstrating a good fit to a linear model ($r^2 \geq 0.8$) in the case of 27 of 29 patients. Assessments of inspiratory resistance may be influenced by a number of factors, including gas flow rates and variations in lung volumes due to gas trapping. Analysis (not shown) of our data suggests that these factors did not appreciably influence the relation between preoperative inspiratory resistance and the postoperative change in expiratory flow rates.

Although plethysmographic measurement of airway resistance during panting is a more common clinical test, we chose specifically to measure lung resistance during spontaneous breathing because a variety of observations suggest that plethysmography may underestimate the contribution of intrinsic airway resistance in patients with severe chronic obstructive lung disease, leading to an inaccurate assessment of airflow obstruction.[18-20]

In addition to having a lower inspiratory resistance, the patients with a response to surgery had a significantly lower transpulmonary pressure at total lung capacity than those without a response. These findings suggest that patients with a greater loss of elastic recoil and greater preservation of airway structure, as indicated by a lower inspiratory resistance, have the best response to lung-volume–reduction surgery. These observations are consistent with the hypothesis that patients with intrinsic small-airway disease, identified in our study on the basis of high inspiratory resistance values, derive less benefit from such surgery.

In addition to measuring resistance, we also measured static elastic properties of the lung in the patients before surgery. Loss of elastic recoil is a prominent feature of emphysema, and surgery to reduce lung volume has been reported to increase elastic recoil.[21] In our analysis, elastic properties alone could not be used to predict postoperative benefit. This finding is consistent with prior reports that showed a poor correlation between the degree of elastic recoil and expiratory flow rates in patients with airflow obstruction.[22,23]

Although promising, our observations need to be extended to a larger group of patients. Further study is needed to establish the relation between preoperative anatomical and physiologic variables and postoperative outcome. Others have reported that anatomical criteria such as an upper-lobe predominance of disease, heterogeneous distribution of parenchymal destruction, and the presence of largely unaffected lung parenchyma also are predictive of postoperative benefit.[24,25] Inspiratory resistance needs to be measured in patients with a heterogeneous distribution of emphysema to establish whether this variable provides additional prognostic information about postoperative benefit in such patients.

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