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Relationship Between Amount of Lung Resected and Outcome After Lung Volume Reduction Surgery

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Background. Lung volume reduction surgery (LVRS) is being actively investigated for palliative treatment of severe emphysema. Considerable focus is directed toward patient selection and outcomes of LVRS. However, there is little information available regarding surgical methods to guide optimal extent of resection. We hypothesized that acute improvement and long-term survival after bilateral staple LVRS would be related to the extent of tissue resected.

Methods. The relationship between acute improvement in forced expiratory volume in 1 second and forced vital capacity was examined as a function of the total grams of lung tissue resected in 237 patients who underwent bilateral staple LVRS by a single group of surgeons. Overall survival was assessed based on extent of resection by quartiles of tissue weight resected using Kaplan-Meier survival methods.

Results. Improvement in forced expiratory volume in 1 second and forced vital capacity correlated with extent of

tissue resected ($p < 0.01$), although there was considerable variability to individual response ($r = 0.3$). In contrast, there was no apparent relationship between the amount of tissue resected and overall postoperative survival ($p = 0.7$).

Conclusions. There is a correlation between the amount of tissue resected and improvement in forced expiratory volume in 1 second and forced vital capacity after bilateral staple LVRS, with generally greater postoperative improvement after larger volume resections. However, there does not appear to be greater long-term survival with larger volume resections despite greater improvement in spirometry. This study suggests that factors other than improvement in spirometric variables may govern optimal LVRS resection volumes and long-term outcome. Future studies will clearly be needed in this important area of LVRS emphysema research.

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Lung volume reduction surgery (LVRS) leads to acute improvement in lung function and dyspnea in selected patients with severe emphysema [1-6]. The ongoing National Institutes of Health-sponsored National Emphysema Treatment Trial will address a number of questions concerning long-term objective and subjective efficacy, survival, and costs of LVRS compared to medical management [7, 8]. However, there is little information concerning methods for optimizing surgical techniques, and the National Emphysema Treatment Trial will not investigate fundamental issues in this area.

One of the first steps that will be required for optimization of lung volume reduction procedures will be to determine relationships between the amount of tissue removed and postoperative outcomes. Surgical LVRS series describe removal of 20% to 30% of the lung volume [1, 9-11]. However, methods for assessing the amount of tissue removed are crude, and the relationship between

the amount of tissue removed and response to operation have not been formally investigated.

The goal of this study was to begin to investigate the relationship between the amount of tissue resected and response to LVRS. We hypothesized that there should be curvilinear relationship between amount of lung tissue resected and response to treatment. Within limits, removal of increasing amounts of lung tissue would be expected to result in greater improvement in spirometry after LVRS. However, beyond some point, lung function would be expected to deteriorate or mortality increase as greater resected tissue volumes would leave too little residual lung parenchyma to function adequately. Analogous predictions would also be made for gas exchange properties and diffusing capabilities of the lung.

Previously, we reported a preliminary correlation between the grams of tissue resected and acute change in forced expiratory volume in 1 second (FEV_1) in a group of patients undergoing unilateral or bilateral staple LVRS [3]. Improvement in FEV_1 after LVRS appeared to correlate linearly with the grams of lung tissue resected over the range of tissue resections in the overall group, with-

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out evidence of deterioration at the highest levels of resection performed. However, that analysis was limited primarily by the mixing of data from unilateral and bilateral LVRS patients. The majority of patients in the lower ranges of resection had unilateral procedures, whereas the higher ranges were bilateral LVRS procedures. Thus, the greater acute benefit of bilateral compared to unilateral LVRS may have affected the apparent overall relationship between grams of tissue resected and acute outcome.

We have now accrued information from a much larger number of patients, all of whom underwent more uniform bilateral video-assisted thoracic surgery (VATS) staple LVRS procedures, with preoperative and postoperative pulmonary function testing and longer term survival information. This cohort enables more meaningful analysis of the correlation between amount of tissue resected and response to LVRS.

In this study we investigated the relationship between amount of tissue resected during bilateral staple VATS LVRS and pulmonary function response, as well as with long-term survival in 237 consecutive patients. The information from this study should be a useful step in the eventual LVRS optimization process.

Material and Methods

Methods for patient selection, preoperative analysis, surgical procedures, and follow-up studies for patients undergoing bilateral LVRS in this clinical program have been previously described [3, 12].

All patients who underwent bilateral VATS staple LVRS at Chapman Medical Center from April 1994 to November 1997 were included in this evaluation. Patients underwent baseline complete pulmonary function testing including spirometry, gas exchange measures (room air arterial blood gas measurement, diffusing capacity of the lung for carbon monoxide), plethysmography, and gas dilution lung volumes. Maximum inspiratory and expiratory flow volume curves, and thoracic gas volume were measured in a plethysmograph (Collins/Cybermedic Classic TCI and Body Plethysmograph, Warren E. Collins, Inc, Braintree, MA), and compared to predicted values as previously described [3, 12]. All patients underwent LVRS at Chapman Medical Center by one of two thoracic surgeons in the research group (RJM, RJF). No procedures were performed at any other center in this protocol.

Repeat pulmonary function studies were requested from patients 3 months after operation, at 6 months, and at approximately 6-month intervals thereafter when obtainable. Whenever possible, repeat spirometry was performed at least once at Chapman Medical Center within 3 months of operation, but subsequent spirometry data were obtained from the referring site.

Informed consent for operation and preoperative evaluation was obtained from all patients. Despite maximal medical management, all patients were markedly symptomatic. Chest radiographs showed hyperexpansion of the thorax with flattening or inversion of the diaphragms.

Inclusion and exclusion criteria have been published

previously [3, 12]. Despite maximal medical management, all patients were markedly symptomatic subjectively, and as measured by dyspnea index and quality of life assessment. Chest roentgenograms showed hyperexpansion of the thorax with flattening or inversion of the diaphragms, assessed qualitatively. To be accepted for the procedure, the pattern of emphysema on computed tomographic scan had to be severe and heterogeneous. Radionuclide lung perfusion scans were also used to confirm the heterogeneous pattern of emphysema.

Contraindications to operation for this study included current cigarette smoking, age more than 80 years, severe cardiac disease (congestive heart failure, significant coronary or valvular disease), history of cancer within the last 5 years, ventilator dependency, or previous thoracic operation. Relative contraindications included age more than 75 years, severe anxiety, severe depression, or carbon dioxide retention with resting arterial carbon dioxide tension more than 55 mm Hg [3, 12].

Thoracoscopic Lung Volume Reduction Operative Methods

Operative procedures for bilateral thoracoscopic staple volume reduction surgery (VATS LVRS) have been previously described as well [3, 12]. Patients underwent VATS under paralyzed general anesthesia using a left-sided double lumen tube (Mallinckrodt Anesthesia; Mallinckrodt, St. Louis, MO).

Procedures were performed in the lateral decubitus position by one surgical group (RJM, RJF). A trocar and thoracoscope were placed through the tenth intercostal space in the posterior axillary line. Three additional 1- to 2-cm incisions were made for standard instruments. Patients were turned to the contralateral decubitus position for separate sterile preparation and draping after completion of operation on the initial side.

Preoperative lung computed tomographic scans and ventilation perfusion scans were used to identify areas of dysfunctional or degenerated lung, which was targeted for staple resection. Ring forceps manipulated the lung into a 60-mm endoscopic stapler (ELC 60, Ethicon, Cincinnati, OH) with bovine pericardium (Peristrips, Biovascular, Saint Paul, MN) or Instat (Johnson and Johnson, New Brunswick, NJ) to buttress the staples. The staples were fired an average of 15 times for bilateral operations. Typically, approximately half of the upper lobe was resected in patients with upper lobe disease.

Grams of Tissue Resected

All excised specimens were weighed after removal from the thorax. The excised specimens included attached bovine pericardial or Instat strips (Biovascular Co, St. Paul, MN) and staples.

Survival

As previously described, survival status was assessed for all patients by contacting them directly or their referring physicians between January and February 1998. The latest date of known survival was recorded, and the date and cause of death (if known) was recorded for patients

who died. Information on cause of death when available was obtained from families or referring physicians.

A total of 12 patients were lost to follow-up as of January 1998. For these patients, the last known date of contact was recorded and used as the censoring date for this study.

Response Assessment

The change in FEV₁, forced vital capacity (FVC), and dyspnea score, at the time of initial follow-up was determined for all patients whose initial follow-up visit was within 1 year of operation. The short-term postoperative improvement was defined as the FEV₁ measured closest to 6 months after operation. Two-year follow-up was determined as the follow-up visit closest to 24 months (between 18 to 30 months).

Statistical Analysis

Baseline characteristic and group descriptive characteristics are reported as mean and standard deviations. The overall survivor function is estimated using the Kaplan-Meier method. Differences in survival after stratification by grams resected quartile levels was tested using the log-rank test (Tarone-Ware). The effect of grams of lung tissue resected on outcome was investigated as a continuous variable using Cox proportional hazards regression. Survival analyses were performed using Kaplan-Meier methods, with Cox proportional hazards analysis. Analyses were conducted using Systat 7.0 for Windows statistical software package (SPSS Inc, Chicago, IL).

Rehabilitation

Patients did not receive preoperative rehabilitation at the Medical Center before LVRS. All patients underwent a similar regimen of pulmonary rehabilitation at Chapman Medical Center beginning immediately after hospital discharge. The rehabilitation consists of a 10-day outpatient regimen involving a multidisciplinary approach with nursing, respiratory, dietary, nutritional, psychosocial, occupational, and physical therapy. Patient education, physical exercise (walking, flexibility, and strengthening), self-monitoring, breathing retraining, and bronchial hygiene instruction are included.

Results

Demographics, baseline characteristics, and response to operation have been previously described in this group of patients [13]. Two hundred thirty-seven patients (85 women, 152 men) underwent bilateral stable LVRS at Chapman Medical Center during the study period. Baseline characteristics and short-term follow-up results of this group have been previously described. Mean age was 67 ± 7 years (range, 38 to 81 years).

The total grams of tissue resected was documented for all patients (Fig 1). Mean grams resected was 124.8 ± 45.8 g (95% confidence interval 118 to 131 g, skewness 1.15). Quartile distributions for grams resected were less than 92 g for the first quartile, 92 to 116 g for the second

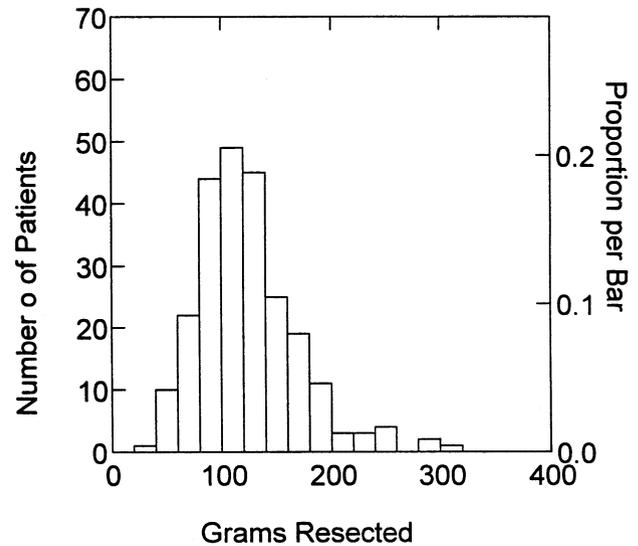


Fig 1. Histogram showing distribution of grams resected for all patients who underwent bilateral staple lung volume reduction surgery (LVRS) in this study. Left axis shows number of patients, right axis shows proportion of total patients. Grams resected is total wet weight of resected tissue including staples and bovine pericardium or Instat.

quartile, 116 to 144.5 g for the third quartile, and more than 144.5 g for the upper quartile.

Baseline Characteristics by Operative Grams Resected Levels

Baseline characteristics were examined for all patients based on operative grams resected levels as a continuous variable (linear regression), and by grams resected quartile level (analysis of variance) (Table 1). As expected, there was a loose but statistically significant association between the amount of tissue resected in grams and preoperative height ($r = 0.22, p = 0.01$) and weight ($r = 0.26, p = 0.001$), with larger resections in the larger patients. Patients with larger baseline total lung capacities also had statistically larger resections ($r = 0.28, p < 0.001$). There was a significant increase in the amount of tissue removed in patients operated on more recently than in those operated on earlier in the program ($r = 0.39, p < 0.001$).

There was no correlation between grams resected and other baseline characteristics or baseline lung function findings (Table 1).

Acute Response Based on Grams of Tissue Resected

Forced expiratory volume in 1 second improved acutely by 0.44 ± 0.03 L (mean FEV₁, 0.63 ± 0.02 L preoperatively to 1.07 ± 0.03 L postoperatively) (Table 2). As a continuous regression variable, there was a significant correlation between the grams of tissue resected and the improvement in FEV₁ postoperatively ($r = 0.26, p < 0.001$, coefficient 2 mL/g resected). Similar results were seen when the relationship between grams resected and FEV₁ response was examined as a percentage of change in FEV₁ from baseline, or change in percent predicted FEV₁.

Table 1. Baseline Characteristics of LVRS Patients: Overall and by Quartile of Grams Resected

Variable	Overall	Grams Resected Quartile 1 (< 92 g)	Grams Resected Quartile 2 (92-116 g)	Grams Resected Quartile 3 (116-145 g)	Grams Resected Quartile 4 (> 145 g)	p Value
Age (y)	66.7 ± 7.0	67.0 ± 0.8	65.0 ± 1.0	67.0 ± 1.0	67.0 ± 1.0	NS
FEV ₁ (L)	0.63 ± 0.01	0.64 ± 0.03	0.60 ± 0.03	0.61 ± 0.03	0.67 ± 0.03	NS
FVC (L)	1.93 ± 0.05	1.91 ± 0.08	1.92 ± 0.10	1.92 ± 0.09	1.98 ± 0.09	NS
TLC (L)	7.24 ± 0.12	6.69 ± 0.23	7.16 ± 0.27	7.30 ± 0.20	7.92 ± 0.25	0.01
RV (L)	4.50 ± 0.10	4.07 ± 0.20	4.61 ± 0.23	4.58 ± 0.17	4.76 ± 0.20	0.08
DLCO	5.14 ± 0.20	5.00 ± 0.40	5.28 ± 0.45	4.82 ± 0.31	5.67 ± 0.38	NS
PO ₂	65.8 ± 0.8	63.3 ± 1.6	67.4 ± 1.8	65.8 ± 1.3	62.9 ± 1.6	NS
PCO ₂	42.5 ± 1.0	42.4 ± 1.0	43.2 ± 1.1	42.5 ± 0.8	41.9 ± 1.0	NS

DLCO = diffusing capacity of the lung for carbon monoxide; lung volume reduction surgery; NS = not significant; residual volume; TLC = total lung capacity. FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; LVRS = lung volume reduction surgery; NS = not significant; PCO₂ = partial pressure of carbon dioxide; PO₂ = partial pressure of oxygen; RV = residual volume; TLC = total lung capacity.

When change in FEV₁ was evaluated based on grams resected quartiles (Table 2), a clear difference is seen among the resection quartiles, with greater FEV₁ response for patients across increasing resections (r = 0.26, p = 0.003 by analysis of variance).

No correlation was seen between the grams of tissue resected and improvement in FEV₁ at 2 years after operation (p > 0.6, n = 87).

Forced vital capacity improved by 0.85 ± 0.05 L (mean FVC, 1.9 ± 0.05 L preoperatively to 2.8 ± 0.06 L postoperatively) after LVRS. Improvement in FVC correlated with the amount of tissue resected (r = 0.28, p < 0.001, coefficient 5 mL/g resected) (Table 2). Again, analogous results were obtained when the correlation between grams resected was examined as either absolute changes, or as percent change from baseline. An incremental increase in FVC was seen with increasing quartiles of resection (Fig 2, r = 0.26, p = 0.003).

Change in FVC at 2 years did not correlate with grams of tissue resected (p > 0.7, n = 87).

Dyspnea score changes postoperatively showed a weak correlation with the amount of tissue resected (Pearson correlation -0.21, p = 0.013). However, once again, no relationship was seen at 2-year follow-up.

Survival Based on Grams of Tissue Resected

OPERATIVE SURVIVAL. There was no difference in acute operative mortality (30-day survival) based on amount of

tissue resected (p = 1.8); however, 30-day mortality was low and relationships could have been missed.

OVERALL SURVIVAL. Kaplan-Meier survival curves for all patients based on total grams resected quartiles are shown in Figure 3. No relationship is seen between amount of tissue resected and overall survival. Covariate analysis to correct for possible influence of confounding variables failed to uncover any relationship between grams resected quartiles and long-term survival.

Covariate analysis using grams resected as a continuous variable with Cox proportional hazard analysis again revealed no evidence of a relationship with long-term Kaplan-Meier survival (n = 237, p = 0.152).

Comment

In this study, we examined the relationship between the amount of tissue resected and outcome after bilateral VATS staple LVRS for treatment of severe emphysema. We found that lung function improvement correlated with the extent of resection, but long-term survival did not.

We had hypothesized that there would be a curvilinear response of lung function or mortality with the amount of tissue resected, with minimal improvement at the lowest resection volumes, moderate to optimal improvement in

Table 2. Response After LVRS: Overall Response and by Quartile of Grams Resected

Change After LVRS	Overall	Grams Resected Quartile 1 (< 92 g)	Grams Resected Quartile 2 (92-116 g)	Grams Resected Quartile 3 (116-145 g)	Grams Resected Quartile 4 (> 145 g)	p Value
FEV ₁ (L)	0.44 ± 0.03	0.30 ± 0.05	0.41 ± 0.06	0.45 ± 0.04	0.55 ± 0.05	0.0005
FVC (L)	0.85 ± 0.05	0.66 ± 0.1	0.83 ± 0.12	0.77 ± 0.09	1.18 ± 0.1	0.003
FEV ₁ (%)	15.1 ± 0.89	12.6 ± 1.8	15.9 ± 2	17.1 ± 1.5	19.4 ± 1.8	0.05
FVC (%)	22 ± 1.3	17.9 ± 2.6	21.6 ± 3	19.9 ± 2.1	29.2 ± 2.6	0.01

FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; LVRS = lung volume reduction surgery.

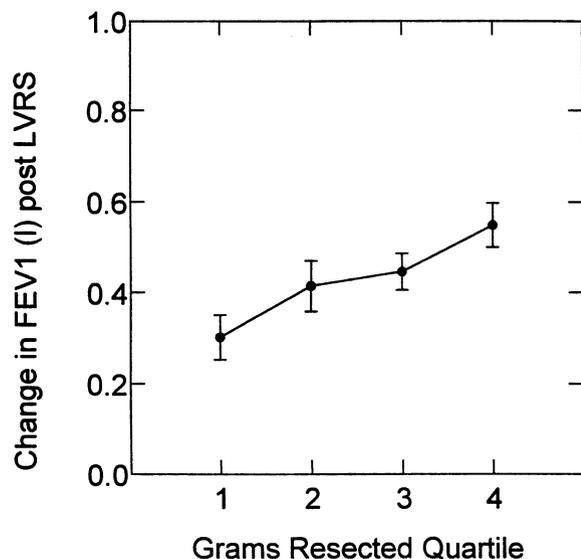


Fig 2. The mean forced expiratory volume in 1 second (FEV1) response to lung volume reduction surgery (LVRS) based on the grams of tissue resected. Mean increase in forced expiratory volume in 1 second is shown on the y-axis. x-axis shows quartile group for grams resected. Quartile 1 = less than 92 g, quartile 2 = 92 to 116 g, quartile 3 = 116 to 145 g, quartile 4 = more than 145 g. $p < 0.001$ for effect of grams resected quartile on forced expiratory volume in 1 second response.

a midrange, and deterioration at excessive resection volumes. There was greater pulmonary function benefit with increasing resection volume, but we did not detect any trend toward decreasing flows even at the highest resection volumes performed in this series. There are a number of possible reasons for this. We measured only change in FEV₁, FVC, and dyspnea score as the pulmonary function outcome variables. One would suspect that some physiologic variables might increase whereas others might decrease with increasing lung resections [14, 15]. The ranges over which these effects are seen will likely vary based on the physiologic outcome variable assessed, and by individual disease presentation. The ranges of resection volumes removed in this study may have been well under the maximal ranges for tolerable flow results, and greater improvement might possibly be expected with even larger resections.

Alternatively, other physiologic variables that were not assessed postoperatively in these patients may have shown deterioration with increasing resection amounts. For example, we speculate that pulmonary vasculature may limit LVRS rather than spirometry in many patients [14]. Because pulmonary circulation information is not available to us postoperatively, it remains possible that pulmonary circulatory variables may have deteriorated at the upper limits of the resection ranges. Pulmonary capillary volume and vascular effects of LVRS would be expected to result from opposing effects of increasing traction on capillary walls versus decreased total capillary numbers with resections. Thus, it may be difficult to predict resection-limiting effects of the pulmonary vasculature a priori.

We also speculated that mortality might increase non-

linearly with increasing lung tissue removal, when limits of tolerability of a physiologic variable are exceeded. It is conceivable that many physiologic responses will appear to be improving with increasing resection, although excessive mortality may occur. Yet, mortality did not correlate with resection volumes, even at the highest resection levels in this study.

There is currently no available method to accurately assess the volume of lung tissue resected. We measured excised tissue weight, yet we know that volume of tissue resected is poorly assessed by excised tissue weight, particularly in severely emphysematous lungs where the most diseased regions contain the most hyperinflated, degenerated tissue. In addition, edema, nodules, and fibrotic tissue tend to increase relative weight to volume ratios of abnormal excised lung regions. Measuring lung volume of resected tissue is not possible, as it is deflated, extrathoracic, and stapled. It is not possible to estimate amount of tissue removed based on differences in lung volume before and after operation because of compensatory changes in the remaining lung. No attempt was made to remove staple or pericardium in the excised tissue, adding to potential measurement bias. No correction was made for the size of the lungs or patient preoperatively in these analyses. Trying to normalize the amount of tissue removed as a fraction of the total lung volume would be a very crude process, with little validation to support it in the literature. Yet, despite the limitations of excised tissue weight as a surrogate for volume of lung tissue resected, we find it to be the most practical tool available to us at this time.

A major limitation of this study is that the extent of lung resected was not randomly assigned [3, 12]. Patients who had larger volumes of lung resected may have had larger regions of distinct heterogeneous lung tissue degeneration. Thus, larger resection volumes may have

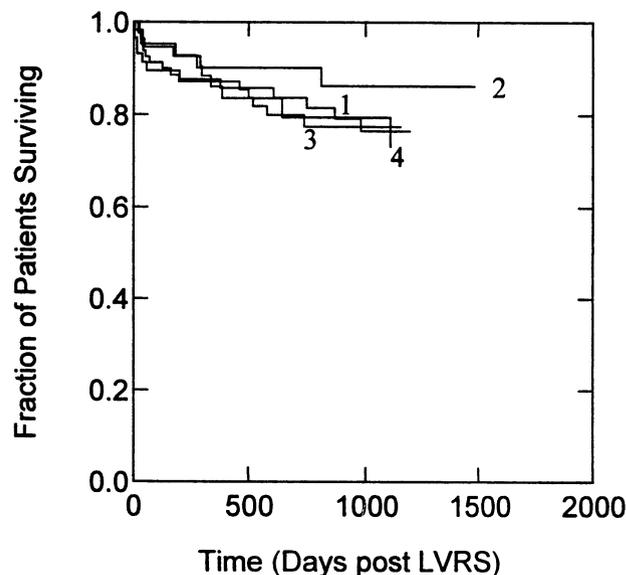


Fig 3. Kaplan-Meier survival curves for patients who underwent bilateral staple lung volume reduction surgery (LVRS) based on grams resected quartile. There is no difference in overall survival associated with operative grams resected quartile.

been markers of more optimal patient presentation and better potential for improvement, rather than a direct effect of the amount of tissue removed.

Within these limitations, the amount of tissue resected correlated with the improvement in lung function after LVRS for patients who underwent bilateral staple VATS LVRS in this series. However, there was no detectable relationship between the amount of tissue resected and long- or short-term survival. This may appear paradoxical as survival has been shown to correlate with improvement in FEV₁ after LVRS in previous studies from our center [13]. However, variability within this relationship probably explains these findings.

In an analogous manner, dyspnea score improvement showed a weak correlation with grams resected, which disappeared by the 2-year follow-up. Acute improvement would be expected to correlate to some degree with the extent of operation. We speculate that longer term results might relate more to rate of deterioration of lung function, which may be dependent on the nature of the underlying lung disease, stress relaxation, or as yet unidentified factors.

Overall, this is the first focused analysis of the relationship between the intraoperative extent of resection and response to LVRS. Although there are considerable limitations, this study demonstrates the great need for further investigations aimed at defining the relationship between resection volume and outcomes after LVRS. Ultimately, this approach should lead to intraoperative methods for optimizing LVRS procedures.

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