

Physiological and Computed Tomographic Predictors of Outcome from Lung Volume Reduction Surgery

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Rationale: Previous investigations have identified several potential predictors of outcomes from lung volume reduction surgery (LVRS). A concern regarding these studies has been their small sample size, which may limit generalizability. We therefore sought to examine radiographic and physiologic predictors of surgical outcomes in a large, multicenter clinical investigation, the National Emphysema Treatment Trial.

Objectives: To identify objective radiographic and physiological indices of lung disease that have prognostic value in subjects with chronic obstructive pulmonary disease being evaluated for LVRS.

Methods: A subset of the subjects undergoing LVRS in the National Emphysema Treatment Trial underwent preoperative high-resolution computed tomographic (CT) scanning of the chest and measures of static lung recoil at total lung capacity (SR_{TLC}) and inspiratory resistance (R_I). The relationship between CT measures of emphysema, the ratio of upper to lower zone emphysema, CT measures of airway disease, SR_{TLC}, R_I, the ratio of residual volume to total lung capacity (RV/TLC), and both 6-month postoperative changes in FEV₁ and maximal exercise capacity were assessed.

Measurements and Main Results: Physiological measures of lung elastic recoil and inspiratory resistance were not correlated with improvement in either the FEV₁ ($R = -0.03$, $P = 0.78$ and $R = -0.17$, $P = 0.16$, respectively) or maximal exercise capacity ($R = -0.02$, $P = 0.83$ and $R = 0.08$, $P = 0.53$, respectively). The RV/TLC ratio and CT measures of emphysema and its upper to lower zone ratio were only weakly predictive of postoperative changes in both the FEV₁ ($R = 0.11$, $P = 0.01$; $R = 0.2$, $P < 0.0001$; and $R = 0.23$, $P < 0.0001$, respectively) and maximal exercise capacity ($R = 0.17$, $P = 0.0001$; $R = 0.15$, $P = 0.002$; and $R = 0.15$, $P = 0.002$, respectively). CT assessments of airway disease were not predictive of change in FEV₁ or exercise capacity in this cohort.

Conclusions: The RV/TLC ratio and CT measures of emphysema and its distribution are weak but statistically significant predictors of outcome after LVRS.

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* A complete listing of the NETT Credit Roster can be found at the end of this article.

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Multiple computed tomographic and physiological measures have been investigated as predictors of outcome from lung volume reduction surgery in single sites with small study cohorts. Data collected during the National Emphysema Treatment Trial allow replication of these studies in a large, well-characterized cohort of subjects with severe emphysema.

What This Study Adds to the Field

Lung recoil and inspiratory resistance were not predictive of surgical outcomes. The residual volume-to-total lung capacity ratio and ratio of upper to lower zone emphysema on computed tomography scan were statistically significantly correlated with improvement in lung function and exercise capacity; however, the magnitude of these correlations limits their use in clinical care.

Lung volume reduction surgery (LVRS) has been demonstrated to be one of the limited therapeutic options that can reduce both morbidity and mortality for selected subjects with severe chronic obstructive pulmonary disease (COPD) (1, 2). However, identifying which subjects will experience the greatest benefit from such intervention and therefore have the best risk-to-benefit ratio for undergoing such a procedure has posed a challenge to clinicians. In the National Emphysema Treatment Trial (NETT), upper lobe-predominant emphysema on computed tomographic (CT) imaging and low exercise capacity were two independent characteristics that identified subjects most likely to have a reduction in mortality as a result of surgery (2). Further work to identify computed tomographic and physiological predictors of surgical outcomes in this cohort has been limited. Identification of additional preoperative predictive measures of subject benefit and ultimately the integration of these measures into a preprocedure assessment that included regional distribution of emphysema and exercise capacity would further optimize patient selection for LVRS.

At the time of enrollment, subjects participating in NETT underwent high-resolution CT scanning of the chest in which quantitative measures of airway disease could be performed. An additional subset of these subjects underwent detailed measures of lung physiology including static lung recoil at total lung capacity (SR_{TLC}) and lung inspiratory resistance (R_I), both of which have been independently evaluated as predictors of surgical

outcomes after lung volume reduction (3, 4). We hypothesized that specific physiological and radiographic metrics of airway and parenchymal structure may refine the ability to predict outcomes from LVRS.

METHODS

Clinical Assessment

All subjects enrolled in the NETT underwent lung function testing including pre- and postbronchodilator spirometry and lung volume measurement (2). Computed tomographic images of the chest were acquired at full inflation with a minimum of 200 mA · seconds and reconstructed using a high spatial frequency algorithm, 1- to 2-mm collimation at 20-mm intervals. Densitometric assessments of the burden of emphysema were performed by the NETT Image Analysis Center (IAC) at the University of Iowa (Iowa City, IA), using a Hounsfield unit (HU) threshold of -950 (%low attenuation area less than -950 HU) as described previously (5, 6). Quantitative measures of emphysema were calculated for both the whole lung and upper, middle, and lower thirds. In the latter case, these regions were defined by equal divisions in cranial-caudal lung height. Discrete measures of airway wall thickness were performed with Airway Inspector (www.AirwayInspector.org) at Brigham and Women's Hospital (Boston, MA) in manually selected airways in the right and left upper lobes and right lower lobes, using the phase congruency method for airway wall segmentation (7). From these measures, the square root of the wall area of a 10-mm lumenal perimeter (Pi10) was calculated as described previously (8). In this way, a subject's CT burden of airway disease could be expressed by a single metric. Additional demographic data such as subject age, sex, and smoking history were collected and available for analysis.

Lung Physiology: Lung Static Recoil and Lung Inspiratory Resistance

Five of the NETT clinical centers participated in the lung physiology substudy. Measurement of SR_{TLC} and lung R_i was performed with an esophageal balloon to measure esophageal pressure as an approximation of pleural pressure (9). This was inserted through the nares to a depth of approximately 40 cm and then inflated with 0.5 cm³ of air. Proper balloon placement was confirmed by observing a negligible change in transpulmonary pressure (P_{tp}) with respiratory efforts made against an occluded airway. Transpulmonary pressures were calculated by simultaneously recording pressure at the airway opening and esophagus (P_{tp} = P_{ao} - P_{es}). Gas flow was measured with a pneumotachometer placed at the mouth. A single measure of lung inspiratory resistance was calculated by the methods previously outlined by Ingenito and colleagues (4). Transpulmonary pressure at full inflation was designated as static lung recoil at TLC (SR_{TLC}). Measures of SR_{TLC} were calculated as the average of up to three subject efforts.

Definition of Outcomes after LVRS

The primary outcomes after LVRS used in this investigation were the observed changes in a subject's FEV₁ and maximal work attained on exercise testing at the 6-month postoperative interval. A secondary outcome was the 6-month postoperative change in the University of California, San Diego (San Diego, CA) Shortness of Breath Questionnaire (UCSD SOBQ) total score. A reduction in the UCSD SOBQ total score equates with a reduction in a subject's sense of breathlessness. In all cases, these changes were calculated as the algebraic difference between the values collected 6 months after enrollment and baseline measures made after pulmonary rehabilitation.

Statistical Analysis

All data are presented as means \pm SD. Upper to lower lung zone ratios of emphysema were calculated by dividing the percent emphysema in the upper zone by the percent emphysema in the lower zone. Spearman correlation coefficients were used to express the strength of the relationships between CT measures of emphysema and airway disease, lung function, and lung mechanics at the time of study enrollment. The 6-month postoperative changes in both FEV₁ and maximal exercise

capacity were examined by univariate and multivariate correlative analysis to these baseline metrics of lung mechanics and both CT emphysema and airway disease. *P* values less than 0.05 were considered statistically significant. Statistical analysis was performed with SAS version 9.0 (SAS, Cary, NC).

RESULTS

This analysis was limited to the surgical arm of NETT (*n* = 608), members of had baseline measurement of lung function, exercise capacity, and questionnaire-based assessments of dyspnea (Table 1). The mean FEV₁% predicted was 26.8 ± 7.4 , with a mean residual volume-to-total lung capacity (RV/TLC) ratio of 0.64 ± 0.08 , mean maximal work of 38.7 ± 21.1 W, and a mean preoperative UCSD SOBQ total score of 61.6 ± 18.1 . Whole lung and regional densitometric measures of emphysema were available for 546 subjects. The mean percent emphysema by CT was $15.9 \pm 10.9\%$ and the mean ratio of upper to lower lung zone emphysema was 9.9 ± 43.5 . Additional quantitative airway analysis was performed on the CT scans of 187 subjects from the NETT Genetics Ancillary Study (2). These measures were expressed as the square root of the wall area of a derived airway with a lumen perimeter of 10 mm (Pi10) and the mean value was 5.1 ± 0.6 mm (8).

Across the 5 centers participating the lung physiology substudy, a total of 115 subjects underwent measures of SR_{TLC} (mean, 9.0 ± 4.1 cm H₂O) and 85 subjects underwent measures of R_i (mean, 7.3 ± 4.1 cm H₂O/L/s). The number of subjects enrolled by center is provided in Table 2 and the overall distribution of data collection in the surgical cohort is shown in Figure 1.

Baseline Measures of Lung Function: Surgical Cohort

In univariate analysis, the RV/TLC ratio was inversely correlated with both baseline FEV₁% predicted ($R = -0.50$, $P < 0.0001$) and maximal exercise capacity ($R = -0.53$, $P < 0.0001$). CT emphysema was weakly correlated with FEV₁% predicted ($R = -0.1$, $P = 0.02$) and exercise capacity ($R = -0.1$, $P = 0.02$) but the ratio of upper to lower zone emphysema was not (FEV₁% predicted: $R = 0.006$, $P = 0.90$; maximal exercise capacity: $R = 0.03$, $P = 0.50$). Lung R_i was of significant correlative value for both a subject's FEV₁% predicted ($R = -0.25$, $P = 0.02$) and maximal exercise capacity ($R = -0.48$, $P < 0.0001$) at study enrollment. Static lung recoil at TLC (SR_{TLC}) was not predictive of either a subject's FEV₁% predicted ($R = 0.04$, $P = 0.66$) or maximal exercise capacity ($R = 0.005$, $P = 0.96$).

TABLE 1. BASELINE DATA FOR NATIONAL EMPHYSEMA TREATMENT TRIAL SURGICAL COHORT COLLECTED AFTER PULMONARY REHABILITATION

Parameter	Mean (SD)
Age, years	66.7 (6.3)
Sex, male	355 or 58%
FEV ₁ % predicted	26.8 (7.4)
Maximum work, W	38.7 (21.1)
UCSD SOBQ score (<i>n</i> = 608)	61.6 ((18.1)
Percent emphysema (%LAA-950) (<i>n</i> = 546)	15.9 (10.9)
Emphysema ratio (<i>n</i> = 546)	9.9 (43.5)
Inspiratory resistance, R _i (<i>n</i> = 85)	7.3 (4.1)
Lung static recoil (<i>n</i> = 115)	9.0 (4.1)
Square root of wall area (<i>n</i> = 187)	5.1 (0.6)

Definition of abbreviations: %LAA-950 = percentage low-attenuation area (less than -950 Hounsfield units); UCSD SOBQ = University of California, San Diego Shortness of Breath Questionnaire.

Unless otherwise indicated, data are provided for 608 subjects.

TABLE 2. DISTRIBUTION OF SUBJECT ENROLLMENT BY CLINICAL CENTER FOR LUNG PHYSIOLOGY SUBSTUDY

Center	Static Recoil (SR _{TLC})	Inspiratory Resistance (R _I)
Baylor College of Medicine	28	29
Brigham and Women's Hospital	30	30
Columbia University	6	6
National Jewish Medical and Research Center	20	20
Temple University	31	0

Values represent the number of subjects enrolled at each center who underwent measures of SR_{TLC} and R_I.

Six-month Change in Lung Function after LVRS

Six months after LVRS, the mean change in FEV₁ for the 495 subjects for whom data were available was 200 ± 240 ml. Within this group, 480 subjects underwent additional exercise testing with a mean improvement of 5.4 ± 14.6 W (Table 3).

Physiological Predictors of Surgical Outcome

The preoperative RV/TLC ratio was weakly correlated to both an improvement in FEV₁ predicted ($R = 0.11$, $P = 0.01$) and change in maximal exercise capacity ($R = 0.17$, $P = 0.0001$). There was no relationship between preoperative measures of either lung R_I or lung SR_{TLC} for either the postoperative change in FEV₁ ($R = -0.17$, $P = 0.16$ and $R = -0.03$, $P = 0.78$, respectively)—results depicted graphically in Figures 2 and 3) or the postoperative change in exercise capacity ($R = 0.08$, $P = 0.53$ and $R = -0.02$, $P = 0.83$, respectively).

Computed Tomographic Predictors of Surgical Outcome

Within the surgical cohort, both the baseline burden of CT emphysema (Figure 4) and ratio of upper to lower zone emphysema were weakly predictive of a subject's change in FEV₁ ($R = 0.20$, $P < 0.0001$ and $R = 0.23$, $P < 0.0001$, respectively) and change in maximal exercise capacity ($R = 0.15$, $P = 0.002$ and $R = 0.15$, $P = 0.002$, respectively). When

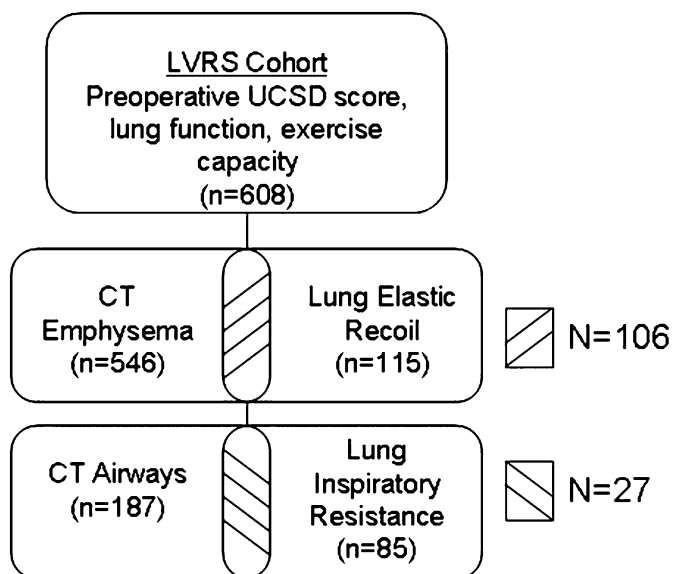


Figure 1. Schematic depiction of preoperative data collected from the surgical cohort. CT = computed tomography; LVRS = lung volume reduction surgery; UCSD = University of California, San Diego Shortness of Breath Questionnaire.

TABLE 3. SIX-MONTH CHANGE IN FUNCTIONAL STATUS OF SURGICAL COHORT

Parameter	Mean (SD)
Δ FEV ₁ , L (n = 495)	0.2 (0.24)
Δ Maximal work, W (n = 480)	5.4 (14.6)
Δ UCSD SOBQ score (n = 507)	-15.5 (22.1)

Changes in parameters were calculated using the measure collected at 6 months minus that collected at baseline.

Data are presented as means and standard deviation.

the RV/TLC ratio, and both CT emphysema and its upper to lower zone ratio, were included in a multivariate model, only the ratio of upper to lower emphysema remained a significant predictor of a subject's change in FEV₁ ($P = 0.0001$, model $R^2 = 0.16$). When using this same model to predict postoperative improvement in maximal exercise capacity, both the RV/TLC ratio and emphysema ratio remained significant ($P = 0.001$ and $P < 0.0001$, respectively; model $R^2 = 0.15$). Finally, in a subset of 177 subjects (only 177 of the original 187 subjects had follow-up lung function testing at 6 mo), CT airway wall thickness (square root wall area of P110) was not predictive of either the 6-month change in FEV₁ ($R = -0.06$, $P = 0.43$) or 6-month change in maximal work ($R = 0.004$, $P = 0.95$).

Predictors of 6-month Change in the UCSD SOBQ Total Score

Six months after LVRS, the mean reduction in UCSD SOBQ total score (signifying an improvement in symptoms) was 15.3 ± 22.1. Within this cohort, preoperative R_I ($R = -0.09$, $P = 0.48$), the total burden of emphysema ($R = -0.04$, $P = 0.35$), and the subject's preoperative SR_{TLC} ($R = -0.11$, $P = 0.32$) were not predictive of improvement in subject symptoms. The preoperative RV/TLC ratio and ratio of upper to lower zone emphysema were both related to a reduction in UCSD SOBQ score at 6 months ($R = -0.14$, $P = 0.02$ and $R = -0.20$, $P < 0.0001$, respectively), suggesting that those subjects with the highest baseline RV/TLC ratio and highest preoperative ratio of upper to lower lung zone emphysema on their CT scan experienced the greatest improvement in symptoms 6 months after LVRS. A subject's improvement in both FEV₁ and maximal exercise capacity was correlated with the reduction in dyspnea ($R = -0.41$, $P < 0.0001$ and $R = -0.5$, $P < 0.0001$, respectively) as assessed by the UCSD SOBQ.

DISCUSSION

Using data from the National Emphysema Treatment Trial, we sought to determine whether detailed physiological assessment of lung function and preoperative high-resolution CT scans of the chest could be used to predict postoperative changes in lung function, exercise capacity, and symptoms of breathlessness. Included in this analysis were the RV/TLC ratio (10, 11) and measures of both the lung static recoil at TLC and lung inspiratory resistance (3, 4). Additional objective CT measures of airway disease as well as both global and regional assessments of emphysema were also used. When examining these metrics on univariate analysis, the baseline RV/TLC ratio and CT measures of emphysema and its distribution were weakly predictive of post-LVRS improvements in lung function and exercise capacity. Further, when adjusted for the total amount of CT emphysema present, only the magnitude of the ratio of upper to lower zone emphysema remained as a significant predictor of 6-month change in a subject's FEV₁. Using a similar model, both the RV/TLC and ratio of upper to lower zone emphysema were predictive of change in maximal exercise

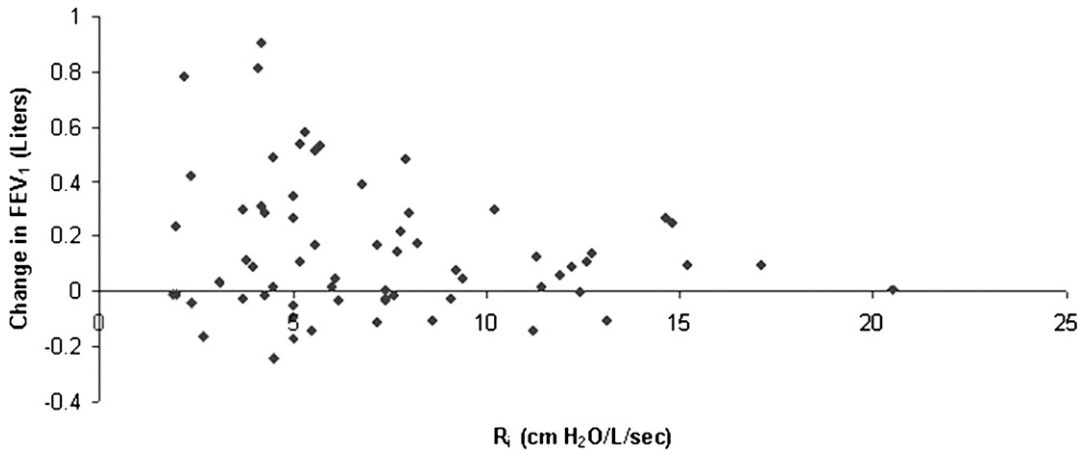


Figure 2. Graphical relationship between a subject's baseline inspiratory resistance (R_i) and their 6-month change in FEV_1 after lung volume reduction surgery.

capacity after LVRS. The preoperative RV/TLC ratio and ratio of upper to lower zone emphysema were both directly related to improvement in symptoms of breathlessness after LVRS.

The lack of correlation between the lung static recoil and either baseline lung function or postoperative change in FEV_1 is consistent with prior observations (4, 12). Preoperative lung inspiratory resistance was, however, expected to be inversely correlated with postoperative improvement in lung function. Those subjects with the highest R_i and therefore the greatest burden of airway disease were expected to have the least functional improvement after LVRS (4). We were unable to confirm this previously demonstrated relationship and, although our findings may suggest that such physiological measures are not predictive of surgical outcomes, it is also possible that this finding is in part due to the difficulties in standardizing physiological data collection across several institutions. Between each NETT center that performed measures of R_i , mean values varied between approximately 3 and 10 $cm\ H_2O/L$ /second. Given the homogeneity of the cohort as a whole, it is unlikely that this difference in R_i reflects true center-to-center variance in subject characteristics. When examining the data from a single center (Brigham and Women's Hospital), the cohort size and distribution of R_i measures (mean R_i , $10.0 \pm 4.2\ cm\ H_2O/L/s$) was similar to that published previously (4), and in this NETT cohort, there was no relationship between preoperative R_i and postoperative improvement in FEV_1 ($R = 0.03$, $P = 0.88$). It should, however, be noted that the cohort members originally described by Ingenito and colleagues (4) were somewhat younger, had more severe airflow obstruction,

less hyperinflation, and different radiographic selection criteria than did NETT participants.

Computed tomographic measures of airspace but not airway disease were found to be predictive of postoperative changes in both lung function and maximal exercise capacity. More specifically, when adjusted for the total amount of emphysema, only the objective ratio of upper to lower zone emphysema on preoperative CT scans was predictive of postoperative improvement. In the original NETT publication, semiquantitative visual determinations of the regional burden of emphysema were found to predict mortality where those subjects with upper zone-predominant disease would have the best chances of experiencing a survival advantage from LVRS (2). Since that time there has been increasing recognition of the interobserver variability in such measures and the potential strength of using objective densitometric measures of emphysema has been emphasized (13). The results of the current investigation suggest that objective measures of the ratio of upper to lower zone emphysema are statistically correlated with surgical outcomes such as improvement in both FEV_1 and maximal exercise capacity. The strength of these observed relationships, however, tempers their use in clinical medicine. These findings are consistent with prior studies such as that reported by Nakano and colleagues, in which the objective ratio of rind to core burden of emphysema in the upper regions of the lung of 21 subjects could be used as a predictor of postoperative improvement in FEV_1 and exercise capacity (14). Although the study by Nakano and colleagues was one of the first to objectively examine the distribution of emphysema in subjects undergoing

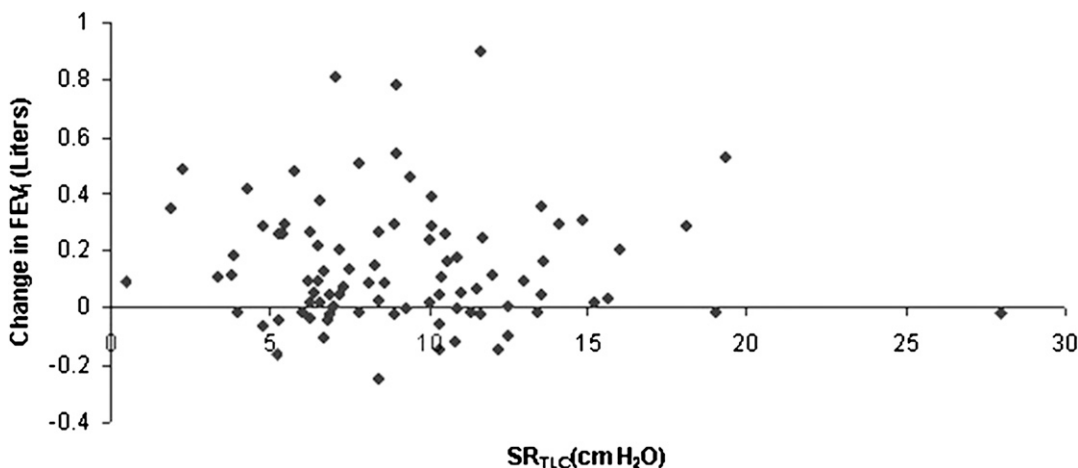


Figure 3. Graphical relationship between a subject's baseline static recoil at total lung capacity (SR_{TLC}) and their 6-month change in FEV_1 after lung volume reduction surgery.

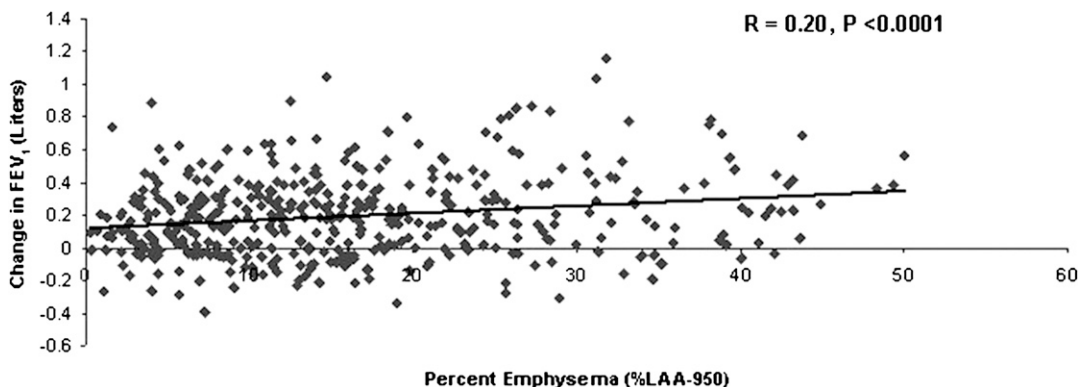


Figure 4. Relationship of the change in FEV₁ (value at 6-mo baseline value) and preoperative percent emphysema (%LAA-950; percentage low-attenuation area [less than -950 Hounsfield units]) as measured from baseline computed tomography scans.

LVRS, additional investigations have reported that both semi-objective measures of disease distribution and quantitative measures of total burden of emphysema could be used as predictors of functional improvement (15–17).

Prior work by Ingenito and colleagues suggests that a subject's burden of airway disease influences outcomes from LVRS (4). On the basis of the reported correlation between CT measures of proximal airways and distal small airway disease (18), we expected to find that those subjects with thicker airway walls on CT scan would experience less functional benefit from LVRS. There was, in fact, no relationship between these measures. The inclusion criteria for NETT, severe COPD and emphysema on CT scan, led to a cohort with emphysema-predominant COPD. This homogeneity of the study cohort and the limited data available in the CT scans may have obscured any such relationship if it existed. An alternative explanation is that there is a predictive relationship between CT measures of airway disease and functional outcomes after LVRS and the metric employed in this investigation, the derived square root of the wall area of a 10-mm luminal perimeter airway, is insensitive to regional burdens of airway disease. For example, a subject with upper zone–predominant emphysema and airway disease may fare better from upper zone volume reduction than a subject with a similar distribution of emphysema but lower zone–predominant airway disease. Such regional discrimination of airway disease and emphysema may have important prognostic implications for such techniques as endoscopic lung volume reduction (19–21). In either case, the age of the CT data and, more specifically, the older generation of CT scanners employed in this investigation with the interval spacing in the reconstructed images limited our analysis and ability to correlate radiographic airway disease and surgical outcomes.

A subject's preoperative RV/TLC ratio was predictive of postoperative improvement in breathlessness. Specifically, those subjects with the greatest hyperinflation on pulmonary function testing experienced the greatest procedurally related symptomatic benefit. Also, computed tomographic measures of a subject's distribution of emphysema but not its absolute burden was correlated with a subject's reduction in dyspnea after surgery. The explanations for these associates are likely found through the stated relationships between these measures and 6-month changes in lung function and exercise capacity.

There are limitations to this investigation that must be acknowledged, including the age of the CT scans undergoing evaluation and the previously mentioned potential difficulty in standardizing measures of lung physiology across multiple centers. In addition, despite this being one of the largest and well-characterized cohorts of subjects with severe emphysema, there was only limited overlap between the CT scans available for objective analysis and measures of both lung elastic recoil and inspiratory resistance.

In summary, objective computed tomography–based measures of emphysema and its upper to lower zone distribution may be predictive of a subject's response to LVRS as assessed by change in lung function and maximal exercise capacity. CT measures of airway disease and physiological measures of lung elastic recoil and inspiratory resistance do not appear to have similar prognostic value. Contrary to earlier reports, R₁ did not predict improvement in pulmonary function or exercise capacity in one of the largest and well-characterized cohorts of subjects with severe emphysema. LVRS is a procedure that can improve quality of life and survival, but only in a highly select group of patients that require careful preoperative physiological and radiologic characterization. This study highlights the complexities of phenotyping patients with COPD. Clearly further investigation is required and a deeper understanding of the pathophysiology of emphysema and its seemingly unpredictable mechanical properties will almost certainly improve clinical decision-making for subjects with severe COPD.

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