Physiological characterization of variability in response to lung volume reduction surgery

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Ingenito, Edward P., Stephen H. Loring, Marilyn L. Moy, Steven J. Mentzer, Scott J. Swanson, and John J. Reilly. Physiological characterization of variability in response to lung volume reduction surgery. J Appl Physiol 94: 20–30, 2003. First published September 20, 2002; 10.1152/japplphysiol.00898.2001.—This paper examines potential physiological mechanisms responsible for improvement after lung volume reduction surgery (LVRS). In 25 patients (63 ± 9 yr; 11 men, 14 women), spirometry [forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC)], lung volumes [residual volume (RV) and total lung capacity (TLC)], small airway resistance, recoil pressures, and respiratory muscle contractility (RMC) were measured before and 4–6 mo after LVRS. Data were interpreted to assess how changes in each component of lung mechanics affect overall function. Among responders (ΔFEV1 ≥ 12%; 150 ml), improvement was primarily due to an increase in FVC, not to FEV1-to-FVC ratio. Among nonresponders, FEV1, FVC, and RV/TLC did not change after surgery, although recoil pressure increased in both groups. Both groups experienced a reduction in RMC after LVRS. In conclusion, LVRS improves function in emphysema by resizing the lung relative to the chest wall by reducing RV. LVRS does not change airway resistance but decreases RMC, which attenuates the potential benefits of LVRS that are generated by reducing RV/TLC. Among nonresponders, recoil pressure increased out of proportion to reduced volume, such that no increase in vital capacity or improvement in FEV1 occurred.

Pulmonary fibrosis is characterized by slow progression of restrictive lung disease, with survival generally decreased by 20–30% after 15 yr (16, 22). Although several studies have attempted to identify functional improvements and clinical outcomes in patients with pulmonary fibrosis, others have suggested that LVRS is not effective in these patients (9–11). Thus, the role of LVRS in pulmonary fibrosis is yet uncertain. Pulmonary fibrosis is characterized by the accumulation of thick collagenous scar tissue that is noncommunicating. This creates an increase in lung “stiffness” (20). Although these arguments are reasonable, clinical observations are not consistent with either of these mechanisms being of physiological importance. Spirometry after LVRS is characterized by similar increases in forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and lung elastic recoil pressure (Pr), but by smaller changes in the FEV1/FVC ratio (1, 4, 6, 9, 14, 16). These observations suggest that LVRS improves function principally by increasing the volume or “amount” of functional lung rather than by altering impedance to airflow. The recent theoretical analysis by Fessler and Permutt (FP; Ref. 5) provides an explanation consistent with these observations. The authors argue that LVRS changes the relationship between the lung and chest wall through a process called “resizing,” in which residual volume (RV) decreases to a greater extent than total lung capacity (TLC). As illustrated in Fig. 1, resizing can increase elastic recoil either with or without an associated change in compliance. In those instances where noncommunicating bullae are resected, post-LVRS compliance is unaffected by resection, but RV and RV/TLC ratio are significantly reduced. The authors suggest that this may be analogous to what happens in patients with heterogeneous, upper lobe-predominant disease in which a nearly parallel shift in lung compliance (CL) to lower volumes occurs (Fig. 1A, response 1), producing a large increase in vital capacity (VC). Alternatively, resizing can occur in a lung with emphysema that is evenly distributed throughout, such that its mechanical properties are homogeneous. Under the assumption that the relationship between pressure and volume after resection remains linear, LVRS would cause a decrease in compliance in proportion to the amount of volume resected (Fig. 1B, response 2). Although this analysis indicates that LVRS

LUNG VOLUME REDUCTION SURGERY (LVRS), originally proposed in the 1950s as a treatment of end-stage emphysema, involves resection of lung that allows space for the remaining lung to function more effectively within the chest cavity (2). Recent studies (1, 3, 8, 9, 11, 13, 20) have documented that after LVRS the average patient experiences significant improvements in expiratory flow rates, quality of life, functional capacity, and dyspnea. However, it is also recognized that responses to this surgery are quite variable. Strategies for identifying optimal LVRS candidates, as well as questions about the durability of benefit and impact on mortality, remain unanswered. A clearer understanding of the physiology underlying LVRS is needed to further optimize patient selection and surgical technique.

It has been suggested that LVRS improves function by tethering “floppy” airways and increasing effective lung “stiffness” (20). Although these arguments are reasonable, clinical observations are not consistent with either of these mechanisms being of physiological importance. Spirometry after LVRS is characterized by similar increases in forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and lung elastic recoil pressure (Pr), but by smaller changes in the FEV1/FVC ratio (1, 4, 6, 9, 14, 16). These observations suggest that LVRS improves function principally by increasing the volume or “amount” of functional lung rather than by altering impedance to airflow. The recent theoretical analysis by Fessler and Permutt (FP; Ref. 5) provides an explanation consistent with these observations. The authors argue that LVRS changes the relationship between the lung and chest wall through a process called “resizing,” in which residual volume (RV) decreases to a greater extent than total lung capacity (TLC). As illustrated in Fig. 1, resizing can increase elastic recoil either with or without an associated change in compliance. In those instances where noncommunicating bullae are resected, post-LVRS compliance is unaffected by resection, but RV and RV/TLC ratio are significantly reduced. The authors suggest that this may be analogous to what happens in patients with heterogeneous, upper lobe-predominant disease in which a nearly parallel shift in lung compliance (CL) to lower volumes occurs (Fig. 1A, response 1), producing a large increase in vital capacity (VC). Alternatively, resizing can occur in a lung with emphysema that is evenly distributed throughout, such that its mechanical properties are homogeneous. Under the assumption that the relationship between pressure and volume after resection remains linear, LVRS would cause a decrease in compliance in proportion to the amount of volume resected (Fig. 1B, response 2). Although this analysis indicates that LVRS

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should increase VC in both instances, the decrease in compliance that accompanies tissue resection in individuals with homogeneous disease would result in a smaller improvement in VC than an equivalent volume reduction in individuals with heterogeneous disease (response 1). This simple but elegant analysis provides a physiological rationale for why patients with upper lobe-predominant disease might derive greater physiological benefit from LVRS than patients with homogeneously distributed disease. However, it does not provide a rationale for why a significant fraction of patients with advanced emphysema that undergo LVRS derive no benefit from the procedure.

Two implicit assumptions of the FP analysis (5) could significantly influence the model's ability to account for the full spectrum of clinical responses observed after LVRS. First, the authors assume that the change in compliance that results from tissue resection in patients with homogeneous emphysema is linearly proportional to the amount of tissue resected. It is possible that, in certain instances, this is not the case, especially when extensive damage to the elastin fiber network has occurred. In damaged tissues, the force-length relationship may be quite nonlinear. In such instances, small changes in length, or volume, could produce disproportionately large changes in force or pressure. If this were to occur, a response similar to that depicted in Fig. 1C, response 3, might be anticipated.

Another assumption of the FP analysis is that respiratory muscle contractility (RMC), described by the active chest wall pressure-volume relationship, is not altered after LVRS. Because RMC is an essential determinant of both TLC and VC, any decline in RMC could attenuate or completely negate the potential benefits of LVRS.

The extent to which these two factors contribute to clinical responses after LVRS is unknown, and either, or both, might account for variability in responses observed among patients who undergo LVRS. To investigate this possibility, flow limitation analysis (15) and the FP model of LVRS (5) were applied to physiological...
measurements made in a cohort of patients before and after LVRS. The measurements and analysis presented here suggest that both of these factors contribute to the physiological responses observed after LVRS, although only the former provides a potential explanation for why certain patients experience an increase in Pr without an improvement in FVC or FEV1.

METHODS

Spirometry, lung volumes, and pulmonary mechanics were measured preoperatively and 4–6 mo post-LVRS.

Subjects. Seventy-seven patients with end-stage emphysema not enrolled in either the National Emphysema Treatment Trial or Overholt Blue Cross Emphysema Surgical Trial clinical trials underwent bilateral LVRS at our institution between October 1994 and June 2000. Twenty-four patients who experienced significant postoperative complications (respiratory failure, persistent air leak, or pneumonia) that could have affected their response to surgical intervention were excluded. Of the remaining 53 patients, 11 men and 14 women (62 ± 8 yr) agreed to participate in this study and completed all aspects of pre- and postoperative testing after giving informed consent in accordance with an institutionally approved human-subjects protocol. All subjects had significant smoking histories (57 ± 18 pack-yr) and functional limitation (Karnofsky scale 72 ± 11%); none had α1 antitrypsin deficiency. Sixteen of the 25 participants used oxygen continuously. All received inhaled β-agonists, and the majority (21/25) received an inhaled anticholinergic and inhaled steroid (19/25). Approximately one-third were receiving theophylline (9/25), and seven patients were taking oral steroids. All patients completed a program of pulmonary rehabilitation before their operation. Surgery. Surgery was performed by one of three surgeons experienced in LVRS. Patients underwent conventional pre-surgical screening that included chest roentgenography, chest computerized tomography scan, quantitative ventilation perfusion scan, pulmonary function testing, transthoracic cardiac echo evaluation, dobutamine stress test evaluation, and 6-min walk. Twenty-four of the 25 patients underwent volume reduction by using the no-cut autologous buttress plication method of Swanson et al. (18), and one patient had two unilateral thoracoscopic procedures that were separated by 9 mo. Average postoperative stay was 9.1 ± 5.4 days.

Physiological measurements. Spirometry was performed after bronchodilator therapy, in accordance with American Thoracic Society guidelines, by using a Morgan Benchmark spirometer. Lung volumes were measured by using a Morgan whole body plethysmograph.

During assessment of detailed lung mechanics, airflow was measured at the mouth by using a Fleisch no. 1 pneumotachometer. Lung volume changes were determined by integrating flow. To minimize errors in volume determinations from gas compression during forced expiratory maneuvers, patients were trained to inhale maximally, then abruptly relax and expire without forceful effort. Maximal expiratory flow rates were achieved without pleural pressures rising to high values, generally <20 cmH2O. Lung volume errors from gas compression, calculated from direct measurements of intrathoracic pressures assuming ideal gas behavior, were 298 ± 144 ml (6.6 ± 2.9% of preoperative RV). These errors were similar in magnitude to intrasubject variation in lung volume determinations; therefore, no corrections for gas compression were made (10).

Pleural pressures were estimated by using an esophageal balloon positioned 40 cm from the nares. Correct balloon position was verified by demonstrating negligible fluctuations in transpulmonary pressure during respiratory efforts against an occluded airway. Static deflation pressure-volume relationships were determined by measuring transpulmonary pressure and expired volume from TLC, with intermittent airway occlusions held for sufficient time to ensure equilibration of airway opening pressure with alveolar pressure. Cl was determined as the ratio of lung volume change to corresponding pressure change between functional residual capacity and functional residual capacity + 500 ml.

Theory. Maximum expiratory flow rate at any lung volume (dV/dt) is the product of the conductance of the airways (Ptm/Gu) and the Pr as it exceeds a “critical closing pressure” for the airways (Ptm’)

\[
dV/dt = G_u(Pr - Ptm') \times 14
\]

For constant Gu and a linear pressure-volume relationship of the lung, maximum expiratory flow decreases exponentially according to the following first-order differential equation

\[
dV(t)/dt = 1/\tau(V(t) - Ptm'G_u)
\]

where τ is the time constant for expiration equal to Cl/Gu (or RuCl; Ru, is the upstream small airway resistance). The solution to this first-order differential equation (Eq. 3 below) represents the volume of gas remaining in the lung as a function of time after initiating a forced expiration in which expiratory flow dynamics is described by Eq. 1

\[
V(t) = VCe^{-\tau t} + Ptm'Cl
\]

The volume V(t) represented in this equation is described by the boundary conditions where V (t = 0) is equal to VC plus the volume of gas trapped in the lung as a result of airway closure, equal to (Ptm’ × Cl), whereas V (t = infinity) is equal to trapped gas volume alone. Expired gas volume (Vexp) at any time (t) is equal to volume at time 0 (VC + Ptm’Cl) minus the volume remaining in the lung as described by Eq. 3 or

\[
V_{exp} = (VC + Ptm'Cl) - (VCe^{-\tau T} + Ptm'Cl)
\]

By setting t = 1 s, FEV1 is obtained

\[
FEV_1 = VC(1 - e^{-\tau})
\]

VC can then be replaced by independent parameters that describe measurable physiological characteristics of the respiratory system

\[
VC = (Ptlc - Ptm')Cl
\]

such that FEV1 can be expressed as a function of TLC pressure (Ptlc), Ptm’, Gu, and Cl.

\[
FEV_1 = [(Ptlc - Ptm')Cl](1 - e^{-\tau})
\]

By expressing the variation in FEV1 as a function of Ptlc, Ptm’, Gu, and Cl by using a Taylor series expansion, changes in FEV1 (∆FEV1) can be described as

\[
\Delta FEV_1 = e^{-\tau}(Ptlc - Ptm')(\Delta Gu - Cl(\tau) + (1 - e^{-\tau})
\]

\[
\times [\Delta (Ptlc - Ptm')Cl + \Delta Cl(Ptlc - Ptm')]
\]

which, in the context of this linearized model, is precisely equivalent to
\[ \Delta FEV_1 = FVC \cdot \Delta(\text{FEV}_1/\text{FVC}) + (\text{FEV}_1/\text{FVC}) \cdot \Delta \text{FVC} \]  

Equation 8 was used to interpret physiological responses to LVRS among our cohort. Terms proceeded by \( \Delta \) represent the difference between the postoperative and preoperative values of a given parameter, whereas terms not preceded by \( \Delta \) represent preoperative values. Results obtained by using this classic flow-limitation approach were also related back to the volume-based analysis of FP to provide insight into how changes in these different parameters relate to one another and are ultimately determined by LVRS.

**Interpretation of results by using the model of FP.** Pleural pressures generated during maximal inspiratory efforts were measured at several lung volumes in each patient to generate a maximum inspiratory pleural pressure-volume relationship for the chest wall. Patients made maximal inspiratory efforts against near-total occlusion at predesignated volumes between TLC and RV as pleural pressure was recorded. Inspiration maneuvers to TLC were then performed without coming off the mouthpiece so that volumes could be accurately referenced. Maximal expiratory flow static Pr (MFSRP) curves were constructed by plotting expiratory airflow vs. elastic Pr by using lung volume as the common reference variable (15). The linear slope of the flow vs. Pr relationship between 30 and 50% of VC was designated as \( G_e \) (or \( 1/R_u \)), the airway conductance upstream of the flow-limiting site (10). The x-axis (Pr axis) intercept was designated as \( P_{tm} \).

Detailed lung and chest wall mechanics were used to assess responses to LVRS by using a Campbell diagram according to the model proposed by FP (5). Active chest wall and lung pressure-volume curves determined pre- and post-LVRS and were plotted as functions of pleural pressure for all patients.

For the purposes of comparison, the cohort was divided into two subgroups of patients. The responder (R) subgroup, which included 17 patients, was defined as those who demonstrated at least a 12% improvement (>150 ml in absolute amount) in FEV\(_1\). The remainder (\( n = 8 \)) were designated as nonresponders (NR).

Results are presented as means ± SD. Significance of changes in physiological parameters after LVRS relative to preoperative values was assessed by paired t-test. Comparisons between R and NR were performed by Student’s t-test where appropriate. Correlations were performed by least-squares linear regression analysis. Statistical significance was defined as \( P < 0.05 \).

**RESULTS**

Changes in spirometry and lung volumes after LVRS.

Pre- and postoperative spirometry values for the cohort and for R and NR subgroups are summarized in Fig. 2, and responses of individual patients in the R and NR groups are summarized in Tables 1 and 2, respectively. Preoperative spirometry demonstrated severe obstruction with an FEV\(_1\) of 0.69 ± 0.26 liter (25 ± 8% predicted), FVC of 2.14 ± 0.69 liters (64 ± 17% predicted), and FEV\(_1\)/FVC of 0.32 ± 0.06. LVRS produced a significant improvement in spirometry. FEV\(_1\) increased by 32% (0.91 ± 0.32 liter, \( P < 0.0001 \)), FVC by 17% (2.49 ± 0.72 liters, \( P = 0.0003 \)), and FEV\(_1\)/FVC by 9% (0.35 ± 0.07, \( P = 0.03 \)).

Among R patients, who represented 70% of the cohort, improvements were more pronounced. FEV\(_1\) increased by 50% (0.64 ± 0.23 to 0.96 ± 0.28 liter, \( P = 0.00006 \)), FVC by 30% (1.99 ± 0.57 to 2.59 ± 0.50 liters, \( P = 0.0002 \)), and FEV\(_1\)/FVC by 12% (0.33 ± 0.07 to 0.37 ± 0.06, \( P = 0.02 \)). Among NR patients, FEV\(_1\) (0.80 ± 0.35 to 0.78 ± 0.39 liter), FVC (2.54 ± 0.86 to 2.50 ± 0.16 liters), and FEV\(_1\)/FVC did not change after surgery.

Lung volume measurements are summarized in Fig. 3. Preoperative lung volumes demonstrated evidence of marked hyperinflation. TLC was 7.26 ± 1.32 liters (136 ± 21% predicted), RV was 5.38 ± 1.24 liters (267 ± 72% predicted), and RV/TLC was 0.74 ± 0.10 (normal range 0.14 to 0.47). LVRS produced a 12% reduction in TLC (6.38 ± 0.99 liters, \( P = 0.0004 \)) and a 22% reduction in RV (4.18 ± 1.07 liters, \( P = 0.0004 \)). RV/TLC also decreased significantly (0.65 ± 0.11, \( P = 0.0037 \)).

Among R patients, significant reductions in both RV (28 ± 13%, \( P < 0.0001 \)) and TLC (14 ± 16%, \( P = 0.0006 \)) were observed in response to LVRS. By contrast, NR patients experienced small reductions in RV and TLC after LVRS that did not achieve statistical significance.

**Chest wall mechanics.** Active chest wall mechanics are summarized in Table 3. RMC is described by the linearized pressure-volume relationship of the chest wall during attempted maximal inspiratory maneuvers against a closed shutter over a range of lung volumes between RV and TLC. LVRS affected chest wall function in two significant ways. First, an increase in maximal inspiratory pleural pressure (MIPP) measured at RV (50 ± 18 to 62 ± 17 cm H\(_2\)O, \( P = 0.0004 \)) was observed. This occurred without an accompanying change in slope of the active chest wall pressure-volume relationship (Ccw-active; \( pre = 0.05 ± 0.02 \) vs. post 0.05 ± 0.02 l/cm H\(_2\)O). However, LVRS was also followed by a significant reduction in the volume intercept of the linear Ccw-active relationship (Ccw-max; \( pre = 7.68 ± 1.25 \) vs. post 6.96 ± 1.07 liters, \( P = 0.0003 \)), such that, at any given lung volume, the abil-
Table 1. Individual responses in the responder group

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Spirometry</th>
<th>Lung Volumes</th>
<th>Flow Limitation Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Pre-op FEV₁</td>
<td>Pre-op FVC</td>
<td>Post-op FEV₁</td>
</tr>
<tr>
<td>1</td>
<td>59</td>
<td>F</td>
<td>0.76</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>M</td>
<td>0.89</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>M</td>
<td>1.12</td>
</tr>
</tbody>
</table>

FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; pre-op, before operation; post-op, after operation; Ptlc, TLC pressure; Ptm, transmural pressure; Gₛ, equal pressure point; γ, time constant.
ity of the chest muscles to generate inspiratory pressure was greater pre-LVRS than post-LVRS.

Similarly, among R patients, a significant increase in MIPP (pre = 48.2 ± 16.3 vs. post = 63.2 ± 16.2 cmH2O) and a decline in Vcw-max (pre = 7.52 ± 1.26 vs. post = 6.71 ± 1.04 liters) were observed after LVRS with no change in Ccw-active. NR patients demonstrated smaller increases in MIPP and reductions in Vcw-max that did not achieve statistical significance.

Static pressure-volume relationships. Pr, as well as static Cw, both changed after LVRS. Pr at TLC (Ptlc) before surgery was 8.4 ± 2.1 cmH2O but increased significantly afterward (11.7 ± 4.0 cmH2O, P = 0.0004). Cw was 0.32 ± 0.17 l/cmH2O preoperatively but decreased significantly in response to treatment (0.23 ± 0.12 l/cmH2O, P = 0.003). Among the R subgroup, responses followed a similar pattern. Ptlc increased from 8.0 ± 1.9 to 11.4 ± 3.5 cmH2O (39%, P = 0.002), and Cw decreased from 0.34 ± 0.19 to 0.25 ± 0.11 l/cmH2O (26%, P = 0.017). Interestingly, similar changes were also observed among NR patients. Ptlc increased from 9.6 ± 2.2 to 12.6 ± 5.3 cmH2O (31%, P = 0.14), and Cw decreased from 0.28 ± 0.11 to 0.15 ± 0.06 l/cmH2O (46%, P = 0.026).

Pride-Permutt analysis. MFSRP relationships were constructed from measurements of static Pr, forced expiratory flow-volume maneuvers, and absolute lung volumes determined via plethysmography. Results for the entire cohort are summarized in Fig. 4. Findings are similar to those previously reported by our group and by others demonstrating that improvements in forced expiratory flows after LVRS are determined almost exclusively by an increase in Pr (7, 10). Ptlc increased without corresponding changes in upstream small airway resistance or Ptm', demonstrating that LVRS had no significant impact on resistance to airflow upstream of the site of flow limitation or gas trapping resulting from airway closure. Similar MFSRP profiles were observed among both R and NR patients.

Campbell diagram analysis. We combine active chest wall compliance data, static lung pressure-volume data, and plethysmographic lung volume measurements in a Campbell diagram to describe the relationship between the chest wall and lung for each patient as FP had proposed in their theoretical manuscript. Results are summarized in Fig. 5. As noted in Chest wall mechanics above, RMC was affected by LVRS such that, although the slope of the relationship between MIPP and chest volume did not change, the intercept of this linear relationship on the volume axis decreased. The increase in MIPP at RV was accounted for by a decrease in retained gas volume. The ability of the respiratory muscles to generate inspiratory force

### Table 2. Individual responses for the non responder group

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, yr</th>
<th>Gender</th>
<th>Pre-op FEV1</th>
<th>Pre-op PVC</th>
<th>Post-op FEV1</th>
<th>Post-op PVC</th>
<th>ΔFEV1</th>
<th>ΔPVC</th>
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<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>M</td>
<td>1.42</td>
<td>3.76</td>
<td>1.59</td>
<td>3.81</td>
<td>0.17</td>
<td>0.05</td>
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<tr>
<td>2</td>
<td>60</td>
<td>M</td>
<td>1.06</td>
<td>3.41</td>
<td>0.76</td>
<td>3.27</td>
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<td>-0.14</td>
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<tr>
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<td>M</td>
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<td>2.08</td>
<td>0.62</td>
<td>2.73</td>
<td>0.00</td>
<td>0.65</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>M</td>
<td>0.92</td>
<td>3.06</td>
<td>0.89</td>
<td>3.33</td>
<td>-0.03</td>
<td>0.27</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>F</td>
<td>0.59</td>
<td>2.15</td>
<td>0.6</td>
<td>1.43</td>
<td>0.01</td>
<td>-0.72</td>
</tr>
<tr>
<td>6</td>
<td>67</td>
<td>F</td>
<td>0.54</td>
<td>1.75</td>
<td>0.6</td>
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</tr>
<tr>
<td>7</td>
<td>58</td>
<td>F</td>
<td>0.46</td>
<td>1.55</td>
<td>0.41</td>
<td>1.01</td>
<td>-0.05</td>
<td>-0.54</td>
</tr>
</tbody>
</table>

Mean ± SD 66.0 ± 5.1 | 0.89 ± 0.35 | 2.54 ± 0.86 | 0.78 ± 0.39 | 2.50 ± 1.06 | -0.92 ± 0.14 | -0.04 ± 0.47

### Lung Volumes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pre-op TLC</th>
<th>Post-op TLC</th>
<th>Pre-op RV</th>
<th>Post-op RV</th>
<th>ΔTLC</th>
<th>ΔRV</th>
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<td>1</td>
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<td>-0.23</td>
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<tr>
<td>3</td>
<td>8.62</td>
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<td>5.26</td>
<td>6.81</td>
<td>0.5</td>
<td>1.55</td>
</tr>
</tbody>
</table>

Mean ± SD 7.51 ± 1.12 | 7.04 ± 0.94 | 5.18 ± 1.31 | 4.96 ± 1.26 | -0.46 ± 0.96 | -0.22 ± 1.09

### Flow Limitation Parameters

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pre-op Ptlc</th>
<th>Pre-op Ptm</th>
<th>Pre-op Gw</th>
<th>Pre-op γ</th>
<th>Post-op Ptlc</th>
<th>Post-op Ptm</th>
<th>Post-op Gw</th>
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<td>4.92</td>
<td>16.2</td>
<td>0.4</td>
<td>0.033</td>
<td>5.04</td>
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<td>0.1</td>
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<td>12.3</td>
<td>1.2</td>
<td>0.12</td>
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<td>0.08</td>
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<td>2.4</td>
<td>0.045</td>
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<td>12.3</td>
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<td>0.1</td>
<td>0.53</td>
</tr>
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</table>

Mean ± SD 9.61 ± 2.18 | 1.23 ± 1.14 | 0.09 ± 0.04 | 3.26 ± 1.01 | 12.64 ± 5.32 | 0.96 ± 1.00 | 0.10 ± 0.05 | 2.41 ± 1.60
was determined by a reduction in CL, not by a parallel VC remained unchanged. The increase in elastic Ptlc and reductions were similar in magnitude. As a result, RV and TLC both decreased minimally, among R patients.

A similar pattern of response is observed after LVRS would, in fact, have been greater had Vcw-max not decreased. The reduction in RV after surgery exceeded the reduction in TLC and resulted in Vcw-max not decreased. The reduction in RV after LVRS would, in fact, have been greater had CL, and Gu after LVRS on forced expiratory flow are summarized in Fig. 6. With the use of the single-compartment flow-limitation model described by Eq. 5, baseline FEV1 was first estimated for each member of the cohort by using preoperative measurements of the four physiological parameters listed above. Predicted changes in FEV1 (ΔFEV1) resulting from LVRS were then estimated by using Eq. 8. Predicted postoperative FEV1 values were calculated by adding to preoperative FEV1 values the model-predictions of ΔFEV1. To assess the utility of the Taylor expansion model for evaluating the contribution of individual changes in Ptlc, Ptm', Cl, and Gu to observed changes in FEV1, we first compared measured changes in FEV1 to changes in FEV1 predicted from Eq. 6 utilizing pre- and postoperative measurements of these independent parameters. Correlation between observed and predicted changes in FEV1 were significant (r = 0.63, n = 25, P < 0.001), suggesting that the Taylor series model, although not exact, accurately represents the relevant physiology.

The effects of changes in Ptlc, Ptm', Cl, and Gu, after LVRS were similarly determined. Results reported for NR patients without an accompanying increase in VC is the physiological basis for why the peak value in expiratory flow (that measured at Ptlc) on the MFSRP plot (Fig. 4C) for NR patients increased, despite a lack of significant improvement in FEV1.

Taylor expansion analysis. To assess the utility of the Taylor expansion model for evaluating the contribution of individual changes in Ptlc, Ptm', Cl, and Gu to observed changes in FEV1, we first compared measured changes in FEV1 to changes in FEV1 predicted from Eq. 6 utilizing pre- and postoperative measurements of these independent parameters. Correlation between observed and predicted changes in FEV1 were significant (r = 0.63, n = 25, P < 0.001), suggesting that the Taylor series model, although not exact, accurately represents the relevant physiology.

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Figure 6 demonstrates two important findings. First, the Taylor series model shows that improvement in FEV1 after surgery would be entirely eliminated if no increase in Ptlc were to occur. Second, the model shows that the improvement in FEV1 after surgery would be greater, not less, if no reduction in Cl were to occur in response to LVRS. This analysis suggests that a reduc-

Table 3. Summary of chest wall mechanics pre- and post-LVRS

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Pre-op MIPP, cmH2O</th>
<th>Post-op MIPP, cmH2O</th>
<th>Pre-op Ccw-Active, l/cmH2O</th>
<th>Post-op Ccw-Active, l/cmH2O</th>
<th>Pre-op Vcw-max, liters</th>
<th>Post-op Vcw-max, liters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort</td>
<td>50 ± 18</td>
<td>62 ± 17</td>
<td>0.05 ± 0.02</td>
<td>0.05 ± 0.02</td>
<td>7.68 ± 1.25</td>
<td>6.96 ± 1.07</td>
</tr>
<tr>
<td>Responders</td>
<td>48 ± 16</td>
<td>63 ± 16</td>
<td>0.05 ± 0.02</td>
<td>0.05 ± 0.03</td>
<td>7.52 ± 1.26</td>
<td>6.71 ± 1.04</td>
</tr>
<tr>
<td>Nonresponders</td>
<td>53 ± 24</td>
<td>60 ± 21</td>
<td>0.06 ± 0.02</td>
<td>0.04 ± 0.01</td>
<td>8.09 ± 1.21</td>
<td>7.62 ± 0.88</td>
</tr>
</tbody>
</table>

Values are means ± SE. MIPP, maximal inspiratory pleural pressure; Ccw-active, change in slope of the active chest wall pressure-volume relationship; Vcw-active, volume intercept of the linear Ccw-active relationship.
tion in Cl after surgery can have a detrimental effect on respiratory function, not a beneficial one.

**DISCUSSION**

Several recent studies suggest that improvement in FEV₁ after LVRS can be primarily attributed to an increase in VC rather than in FEV₁/FVC (1, 8, 10, 16). This simple clinical observation indicates that LVRS improves function principally by reducing RV and increasing VC rather than by altering expiratory lung impedance. These findings are consistent with the physiological model recently proposed by FP that asserts that improvement in lung mechanics after LVRS is due to resizing of the lung and chest wall where the resizing process is specifically associated with a reduction in RV (Fig. 1). At baseline, the overexpanded lung is envisioned as being too large for the chest and thus incapable of expanding to a volume at which Pr are sufficient to generate adequate expiratory flow rates to empty the lungs. After LVRS, the reduced lung size allows more effective expansion, higher Pr, and more complete emptying. The difference between the compliance of the active chest wall, which is relatively stiff, and the emphysematous lung, which is relatively compliant, results in VC being reduced to a greater extent than TLC.

In theory, the benefits of LVRS should occur whether tissue destruction is heterogeneously or homogeneously distributed. In the former case, the ability to resect noncompliant bullae generates a reduction in RV with little accompanying change in Cl. This situation is represented by response 1 of Fig. 1A; the improvement in VC is maximal in this case. In homogeneous disease, resection of tissue produces a similar reduction in RV, but the beneficial effects on VC are not as great since resection of tissue is accompanied by a proportionate decrease in Cl (response 2, Fig. 1B). This change in lung stiffness affects the recoil force that opposes the outward pull of the respiratory muscles to determine TLC. When that force is increased, TLC is decreased as is the improvement in VC. As a result, the benefits of resizing after LVRS are predictably smaller in patients with homogeneous disease, which is consistent with findings of several cohort studies (12, 17). In both heterogeneous and homogeneous disease, this model provides a physiological rationale for the increase in VC that follows LVRS. However, the model does not provide a theoretical explanation for why many patients who undergo LVRS simply fail to improve.

By analyzing and comparing detailed physiological measurements from patients who both did and did not improve their spirometry at 6 mo after LVRS, we detected a pattern of response that is not accounted for by the FP analysis but is characteristic of NR subjects. This pattern is shown in Fig. 1C, response 3, and Fig. 5C and is characterized by a small reduction in RV, disproportionate increase in Pr, and an unexpected large reduction in TLC, such that VC does not increase. Two distinct characteristics of the NR response are noteworthy. First, despite undergoing a volume reduction procedure in which 20–30% of tissue was resected, RV was minimally reduced at 6 mo follow-up. Because a reduction in RV is essential for effective volume reduction, these patients understandably benefited little from the procedure. This observation could point to a difficulty in preoperative evaluation among this particular subgroup, such that the tissues selected for resection failed to substantially reduce RV because those expanding into the vacated space also contributed to RV. This might occur either immediately after surgery because of reexpansion of existing damaged tissues or shortly thereafter through generation of new bullous lesions over a period of several months.

The second interesting characteristic of the physiological response in this subgroup was that failure to improve lung function was not simply due to a failure to change lung mechanics. In fact, a discernible change among NR patients was observed in which Pr increased but VC failed to improve. As indicated above, the increase in stiffness detected among this cohort was out of proportion to the change expected from the small decrease in lung volume, suggesting that the intrinsic mechanical properties of the fiber network in the remaining lung tissue in this group might in fact be different from those in LVRS R subjects. The force-length relationship for lung parenchymal strips has been described by the exponential expression

\[ F(L) = c(L/L_a - 1)e^{a(L/L_a - 1/2)} \]  

(Fig. 4. Average maximal flow static recoil pressure relationships for the entire cohort (A), responder (B), and nonresponder (C) groups. Responses among all 3 groups were similar. Elastic recoil pressure at high lung volumes increased in all 3 groups after surgery and accounted for the observed increases in flow rates, but the slope of the line, which represents conductance of the upstream airways, did not change.)
where $F$ is force, $L$ is length, $L_0$ is optimal muscle length, and $\alpha$ is a coefficient describing the nonlinear relationship between force and length during stretching of lung tissue. This relationship embodies the combined mechanical characteristics of the collagen-elastin network, and for small strains is nearly linear since

$$e^x = 1 + x + x^2/2! + \ldots$$

and

$$e^x \approx 1 + x \quad \text{for} \quad x \ll 1$$

For a volume reduction procedure of 30%, $L/L_0$ is on the order of 10%. For normal tissue $c \approx 1$ and $\alpha \approx 2.6$. In this case, LVRS would increase recoil force ~3%. If the damaged parenchyma in the emphysema lung were to have half as many fibers, such that each fiber is strained twice as much to accommodate the resizing process, and the tissues themselves were composed differently due to selective loss of elastin, such that their force-length relationship was more nonlinear (i.e., $\alpha = 4.6$ rather than 2.6), then the force increase resulting from a 30% volume reduction could be 20%. Although speculative, this argument, which attributes the large changes in $Pr$ in NR patients to nonlinear characteristics of the damaged parenchyma in this patient subgroup, is consistent with the histological changes in the emphysema lung and mechanical properties of lung tissues, and could, at least in part, provide an explanation for the unusual response to LVRS observed in NR patients.

An additional characteristic of the LVRS response, observed among both R and NR patients, was apparent from applying the FP model to our data and appears to have a significant effect on the physiological response to this procedure. The sudden decrease in chest wall volume.

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Fig. 5. Average data for the entire cohort (A), responder (B), and nonresponder (C) groups are presented by using the Fessler-Permutt modeling approach. For the cohort and responder subgroups, LVRS produced 2 clear effects. First, leftward shifts in the pressure-volume relationship of the lung were observed, which was consistent with resizing. However, a second finding was also noted. The pressure-volume relationship of the active chest wall also shifted downward because of a decrease in $C_L$ (the volume intercept of the linear relationship). This represents a decrease in the respiratory muscles to generate negative pressure at iso-volume after LVRS. Its effect is to attenuate the benefits of the resizing process by reducing TLC and VC postoperatively. In nonresponder patients, small changes in RV were accompanied by equivalent changes in TLC, such that VC did not increase. A similar, although less pronounced, effect of LVRS on respiratory muscle contractility was observed among nonresponder patients as reported above for responder patients. CW, chest wall volume.

Fig. 6. Predicted $FEV_1$ as determined from the Taylor expansion model by using measured pre- (preop) and postoperative (postop) physiological. Preop $FEV_1$ is predicted from Eq. 5. Postop $FEV_1$ is based on Eq. 5 when the effect of changes in $G_u$, pressure at TLC, critical closing pressure for the airways ($P_{tm}'$), and $C_L$ are included into the model by using Eq. 6. Subsequent $FEV_1$ predictions show the effects of elimination of the change in a single component of the physiological response. Elimination of the effects of increased recoil pressure (No PTLC) would eliminate the improvement in $FEV_1$, whereas elimination of the decrease in $C_L$ would augment the improvement in $FEV_1$. Together, these results suggest that only those increases in pressure at TLC from resizing have a beneficial effect on lung function.
size that follows LVRS appears to alter respiratory muscle mechanics such that, at a given lung volume corresponding to a given level of stretch, active force generation is less post-LVRS than pre-LVRS. As shown in Fig. 5, this is not due to a change in slope of the pressure-volume relationship for the active chest wall but rather to a decrease in Vcw-max, which represents the point of intercept of the line describing the pressure-volume relationship with the volume axis. The basis for this decline in RMC at isovolume is not clear but appears to occur in proportion to the magnitude of reduction in volume subsequent to the procedure. In our cohort, the decline in Vcw-max was substantially larger among R patients (11%) than among NR patients (5%), as was the reduction in RV. This loss of force-generating ability at isovolume may relate to adaptive changes in the resting length of the respiratory muscles that develop over time in patients with chronic hyperexpansion and are abruptly altered by the procedure. It is also possible that changes in radius of curvature of the diaphragm resulting from the procedure might alter the transdiaphragmatic pressures that can be generated for a given level of contractility. Independent of mechanism, the effect of this loss in isovolume RMC is to cause an attenuation in the potential response to LVRS. As shown in Fig. 5, the decrease in Vcw-max resulted in a substantial reduction in VC that would have occurred had Vcw-max not declined after the procedure. The effect of the change in Vcw-max is to reduce Ptlc, and this effect is thus implicit in the Taylor expansion model result summarized in Fig. 6.

This model highlights several additional points regarding physiological responses to LVRS in terms of the familiar parameters of resistance, compliance, and flow that are, in fact, more clearly described by the pressure, volume, and compliance approach of FP (5). The Taylor expansion model, which predicts how individual changes in Ptlc, Ptm’, Gu, and Cl affect expiratory flow after LVRS, demonstrates that, without an increase in Pr, no improvement in FEV1 would occur. Furthermore, the model provides a straightforward explanation for clinical observations showing that improvement after LVRS correlates with preoperative inspiratory conductance (equivalent to Gu). The physiological parameter in Eq. 8 that changes the most in response to LVRS is Ptlc, which is weighted by Gu through the \(1 - e^{-1/\nu_0}\), which to first order is equal to \(1 - 1/Gu + Gd/Cl + \cdots\) or simply \(Gd/Cl\). Although true, Fig. 6 fails to provide any insight into the true physiological basis for this observation. However, the explanation is readily apparent in the context of FP. An increase in Pr is associated with an improvement in FEV1, but that increase must occur in a very specific context. FP demonstrate what the nature of that increase must be, as exemplified by Fig. 1, A and B, responses 1 and 2. In both of these instances, an increase in Pr is associated with resizng and a reduction in RV. This resizing is responsible for the increase in Pr, VC, and FEV1. These responses are consistent with those observed among R patients in this study. Response 3 (Fig. 1C) also shows an increase in Pr, but with an associated decline in Cl and no improvement in VC. This type of response is similar to that observed among our NR patients who did not improve their FEV1. Thus beneficial effects of LVRS associated with a change in Pr relate specifically to a reduction in RV and not to changes associated with a decrease in compliance.

As mentioned above, NR subjects who demonstrated no improvement in FEV1 still demonstrated an increase in Pr after LVRS. Comparison of MFSRP relationships does not, in fact, allow one to readily discriminate between R and NR subjects in this cohort. Both subgroups demonstrated similar increases in Ptlc after LVRS without changes in expiratory resistance. Figure 5 provides a clear explanation for why similar increases in Pr were associated with such distinct physiological responses to LVRS. Among NR subjects, Ptlc increased but was associated with a decrease in Cl. Only a small reduction in RV occurred, and there was no downward parallel shift in compliance curve. By contrast, as mentioned above, among R subjects, Ptlc increased primarily as a consequence of a reduction in RV, with an accompanying compliance curve shift.

In addition to providing physiological insight into the complexity of responses to LVRS that can be observed clinically, this analysis provides a framework for understanding how the classic maximal expiratory model of flow limitation developed by Pride et al. (15) relates to the Campbell diagram approach developed by FP. This analysis is derived from both approaches and indicates that, although convention has been to describe the physiology of emphysema in terms of flows (FEV1), the critical determinant of change in function after LVRS is volume, specifically VC. The flow-based analysis represented by Eqs. 5 and 7 describe FEV1 in terms of independent parameters that can be readily measured and characterize the function of the respiratory system. However, these parameters are themselves implicitly determined by the static lung volumes of the lung and chest wall described by FP. Thus a simultaneous look at both approaches provides insight into how they relate to one another, while pointing out the profound importance of the FP volume-based approach.

In summary, the data presented here provide direct physiological confirmation for the arguments of FP but also contribute further to our understanding of how LVRS works. They demonstrate that lung resizing associated with a decrease in RV is essential for improvement after LVRS and that increases in Pr per se do not determine improvement. They further suggest that, in some patients, substantial increases in Pr can occur with only small reductions in RV and minimal improvement in VC. This disproportionate increase in pressure may be due to nonlinear force-length characteristics of the damaged lung parenchyma that, after LVRS, are not associated with spirometric improvement. The results also indicate that changes in chest wall RMC, due specifically to a change in Vcw-max, are consistently observed and appear to occur in proportion.
REFERENCES


