Quantitation of Regional Ventilation During the Washout Phase of Lung Scintigraphy*

Measurement in Patients With Severe COPD Before and After Bilateral Lung Volume Reduction Surgery

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Study objectives: We sought to investigate the effect of lung volume reduction surgery (LVRS) on regional lung ventilation.

Design: Retrospective analysis of routinely acquired data before and after LVRS.

Setting: Large, urban, university medical center.

Patients: Twenty-nine patients with severe emphysema.

Intervention: Bilateral LVRS.

Measurements and results: 133Xe washout curves during lung scintigraphy exhibit a biphasic pattern (the first component of the washout curve [mr] corresponds to an initial rapid phase in washout that reflects larger airways emptying, and the second component [ms] reflects a slower phase of washout that is attributed to gas elimination via smaller airways). We analyzed six standardized regions of the lung (upper, mid, and lower zones of the right and left lung), and calculated mr and ms for each lung region. The mean (± SE) baseline FEV1 was 0.69 ± 0.04 L, total lung capacity (TLC) was 139 ± 4% predicted, and the residual volume (RV)/TLC ratio was 65 ± 2%. The mean improvement in FEV1 3 months post-LVRS was 38%. Post-LVRS, mr and ms increased in 79 and 74 lung regions, respectively, and there was no relationship with respect to lung regions that had or had not been operated on. The increase in ms, however, significantly correlated with the increase in FEV1 (r = 0.66; p < 0.0001) and the decrease in RV/TLC (r = −0.67; p < 0.0001). An increase in ms also correlated with a decrease in PaCO2 (r = −0.39; p = 0.03), but mr showed no relationship with any parameter.

Conclusions: Small airways ventilation in lung regions that had and had not been operated on is associated with a greater improvement in lung mechanics following LVRS.

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Key words: emphysema; lung scintigraphy; lung volume reduction surgery; ventilation

Abbreviations: FEF25–75% = forced expiratory flow between 25% and 75% of maximal expiratory flow; FEF50% = forced expiratory flow at 50% of maximal expiratory flow; FIO2 = fraction of inspired oxygen; HRCT = high-resolution CT; LVRS = lung volume reduction surgery; mr = first component of the washout phase; ms = second component of the washout phase; 6MWD = 6-min walk distance; RV = residual volume; TLC = total lung capacity; V/Q = ventilation/perfusion

Lung volume reduction surgery (LVRS) is thought to enhance airway conductance by increasing lung elastic recoil. This improvement is thought to occur at the level of the small airways; however, little information exists to support this contention. Moreover, the current methods of assessing regional lung function and small airways function are limited. Spirometry provides information about global lung airflow. Emphysema, however, rarely affects the entire lung homogenously. An evaluation that characterizes regional lung function may be more valuable than spirometry in assessing the effects of LVRS on regional lung function.

Lung scintigraphy has evolved as a useful clinical tool to assess lung ventilation and is particularly sensitive in the detection of obstructive lung dis-
Materials and Methods

Patient Selection

Patients who underwent LVRS at Temple University Hospital between February 1995 and April 1997 are included in this analysis. Patients were enrolled into the LVRS program after meeting the specified enrollment criteria (Table 1). After informed written consent, all patients underwent 6 to 8 weeks of pulmonary rehabilitation just prior to LVRS. This study was approved by our institutional review board.

Lung Imaging

High-resolution CT (HRCT) scanning (PQ 5000 scanner; Picker Corp; Cleveland, OH, and GE Highlight Advantage; General Electric; Milwaukee, WI) was performed preoperatively using 1.5-mm collimation at 10-mm intervals from the lung apices to the lung bases.

Pulmonary scintigraphy was performed using a large-field-of-view gamma camera (GE 535; General Electric) interfaced to a computer acquisition work station (Nuc Lear Mac; Scientific Imaging; Denver, CO). Ventilation lung images were acquired in the posterior projection during inhalation, equilibration, and washout of $^{133}$Xe gas. For the inhalation phase, 10 mCi of $^{133}$Xe gas was introduced into a closed rebreathing system (Ventil-Con II; Radi; Houston, TX), and the patient breathed at the usual rate as computer images were acquired at 4-s intervals for 16 s (wash-in phase). With the patient still breathing at the usual rate, a 3-min equilibration phase was recorded with the patient rebreathing a mixture of room air and Xe gas. This was followed by a washout phase during which the patient inspired room air, and the expired $^{133}$Xe and room air mixture was vented to a charcoal trap ventilation system. Washout images were recorded every 30 s for a total of 4 min. All images were acquired in a 128 × 128-byte mode matrix. Following the ventilation study, perfusion images were acquired after the IV administration of 4 mCi $^{99m}$Tc-macroaggregated albumin. All images were in a 128 × 128-word matrix for 500,000 counts.

Lung-imaging studies were performed approximately 4 to 6 weeks prior to LVRS and then 3 months following LVRS. Preoperative and postoperative ventilation-perfusion (V/Q) scans in a representative patient are shown in Figure 1. The lung-imaging studies all were performed while the patients remained in stable condition and were performed within 2 weeks of the pulmonary function studies

Operative Procedure

The operative methods for LVRS included the following: (1) biapical resection, the removal of emphysematous lung tissue using a linear stapling device via a standard median sternotomy or sequential video-assisted thoracotomy; and (2) nonapical resection, the removal of the worst emphysematous portions of each lung, regardless of location. Regardless of which of the two operative methods was used, 30 to 50% of the volume of each lung was surgically resected. The areas targeted for resection were based on a preoperative determination of the worst areas of emphysema, determined by experienced thoracic radiologists and nuclear medicine physicians, using visual inspection and quantitation of lung perfusion scans and HRCT scanning. The same cardiothoracic surgeon (S.F.) performed LVRS in all patients.

Analysis of Ventilation Scans

The $^{133}$Xe lung images were divided into six equally sized regions using computer manual regions of interest that were superimposed on both the pre-LVRS and post-LVRS scans. For each of the six regions, the computer generated time/activity curves (Fig 2) with the activity in each region expressed as counts per second. Accordingly, a biexponential curve was fit to the washout data:

$$A_t = A_{se}e^{-mr(t)} + A_{ms}e^{-ms(t)}$$

where $A_t$ is activity in the lung region at any time $t$, $A_{se}$ is the coefficient of the rapid component, and $A_{ms}$ is the coefficient of the slow component, using a data analysis and graphing software tool (KaleidaGraph; Synergy Software; Reading, PA). To confirm the validity of the biexponential model, washout data were

<table>
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<th>Inclusion criteria</th>
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<tr>
<td>New York Heart Association class III–IV</td>
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<tr>
<td>Evidence of airflow obstruction and hyperinflation by pulmonary function studies (ie, postbronchodilator FEV1 &lt; 30% of predicted, and FRC or TLC &gt; 110% of predicted)</td>
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<tr>
<td>Hyperinflation documented by chest radiograph and diffuse bullous emphysema documented by HRCT scan</td>
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<td>V/Q heterogeneity documented in planned resected lung tissue by quantitative ventilation perfusion lung scan</td>
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<tr>
<th>Exclusion criteria</th>
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<tr>
<td>Patients with severe and refractory hypoxemia (PaO2/FiO2 ratio &lt; 150)</td>
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<tr>
<td>Respiratory failure requiring mechanical ventilation</td>
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<tr>
<td>The presence of severe cardiovascular disease</td>
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<td>The presence of severe pulmonary hypertension (mean pulmonary artery pressure &gt; 35 mm Hg)</td>
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<td>Severe debilitated state with total body weight &lt; 70% of ideal expected to limit survival</td>
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<tr>
<td>Psychosocial dysfunction</td>
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<td>Continued smoking</td>
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*FRC = functional residual capacity.
analyzed by a software program (DIMSUM [J DiStefano III]; Biocybernetics Laboratory, University of California; Los Angeles, CA) for optimal fit to a multiexponential function using statistical and goodness-of-fit criteria. The best fit was to a sum of two exponentials.

Lung Function Measurements, 6-Min Walk Test, and Arterial Blood Gas Analysis

Spirometry and lung volume determination were performed using both the gas dilution method and body plethysmography (System 6200 Autobox DL plethysmograph; SensorMedics; Yorba Linda, CA) under standard American Thoracic Society guidelines. Post-bronchodilator values are reported. The usual parameters of airflow obstruction (ie, FEV₁, forced expiratory flow between 25% and 75% of maximal expiratory flow [FEF₂₅–₇₅%], and forced expiratory flow at 50% of the maximal expiratory flow curve [FEF₅₀%]) and of gas trapping (residual volume [RV]/total lung capacity [TLC] ratio) were examined.

On a separate day, the total distance that the patient was able to ambulate in a corridor for 6 min was recorded as the 6-min walk distance (6MWD).

Arterial blood gas was sampled from the radial artery with the patients seated 20 min after receiving a bronchodilator and breathing room air.

Follow-up

Lung scintigraphy and pulmonary function studies were repeated at 3 months post-LVRS in the same manner as pre-LVRS (ie, within 2 weeks of one another) and while the patients were in stable condition.

Determination of Regions of Resection and Correlation With Physiologic Parameters and Washout Components

Operative reports were reviewed to determine the actual areas of the lung resected. In each operative report, the surgeon indicated the location and extent of resection. The terms used were either “wedge resection” or some numeric estimate (eg, “40% of the right upper lobe”). Regions were considered operated on when so indicated in the operative report. The six regions used in the analysis of the ventilation scans corresponded to the upper and lower lobes, as indicated in the operative report. The middle regions on both the left and right were considered operated on if either the operative report indicated right middle lobe resection (one patient) or if the report stated that ≥50% of an upper lobe was resected. Changes (ie, >10% of the pre-LVRS value) in m₀ and mₘ then were correlated with physiologic parameters and the regions of resection.

Statistical Analysis

Data are expressed as mean ± SD except where otherwise noted. All statistical analyses were performed using a commercially available software program (SigmaStat, version 2.0; SPSS; Chicago, IL). Student’s paired t test was used to compare physiologic parameters before and after surgery. Relationships between parameters were determined using Pearson’s correlation.

Results

Eighty-seven patients underwent LVRS. Fifty-eight patients were not included in this study for the
following reasons: 30 patients did not have post-LVRS follow-up ventilation scans; 12 patients died prior to obtaining a follow-up ventilation scan; 9 patients did not have ventilation scans digitized for analysis; 5 patients did not have pre-LVRS ventilation scans because they were receiving mechanical ventilation just prior to LVRS; and 2 patients had LVRS following lung transplantation. Twenty-nine patients (mean age, 56 ± 9 years; 16 women) who underwent LVRS and post-LVRS lung ventilation scans available for analysis and, therefore, are included in this study.

**Effect of LVRS on Ventilation Washout Parameters**

The overall (all regions in all patients) mean values for rapid component of washout ($m_r$) and the slow component ($m_s$) pre-LVRS are 1.4% and 0.8% of maximum activity per second, respectively. Following LVRS, $m_r$ decreased to 1.2% of maximum activity per second ($p = 0.03$), while $m_s$ remained unchanged (0.8% maximum activity per second; $p = 0.9$).

The values for $m_r$ increased in 79 regions (45%), and those for $m_s$ increased in 74 regions (43%). The combined values for $m_r$ and $m_s$ increased in 34 regions (19%). The mean numbers of regions with an increase in $m_r$ and $m_s$ per patient were 2.7 and 2.6, respectively. For the regions that showed an increase in $m_r$, the mean pre-LVRS value was 0.8% maximum activity per second, and the mean post-LVRS value was 1.6% maximum activity per second ($p < 0.001$). For the regions that showed an increase in $m_s$, the mean pre-LVRS value was 0.4% maximum activity per second, and the mean post-LVRS value was 1.3% maximum activity per second ($p < 0.001$). This represented a greater than twofold increase in the magnitude of $m_s$ following LVRS.

**Table 2—Relationship Between Ventilation Washout and Physiologic Parameters Post-LVRS**

<table>
<thead>
<tr>
<th>Physiologic Parameter</th>
<th>Washout Parameter</th>
<th>$r$ Value</th>
<th>$p$ Value</th>
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<tbody>
<tr>
<td>FEV1</td>
<td>No. regions $m_r$ increased</td>
<td>−0.19</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>No. regions $m_s$ increased</td>
<td>0.66</td>
<td>0.00009</td>
</tr>
<tr>
<td>RV/TLC ratio</td>
<td>No. regions $m_r$ increased</td>
<td>0.20</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>No. regions $m_s$ increased</td>
<td>−0.67</td>
<td>0.00006</td>
</tr>
<tr>
<td>FEF25–75%</td>
<td>No. regions $m_r$ increased</td>
<td>0.01</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>No. regions $m_s$ increased</td>
<td>0.43</td>
<td>0.02</td>
</tr>
<tr>
<td>FEF50%</td>
<td>No. regions $m_r$ increased</td>
<td>−0.05</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>No. regions $m_s$ increased</td>
<td>0.49</td>
<td>0.007</td>
</tr>
<tr>
<td>PaCO2, % change</td>
<td>No. regions $m_r$ increased</td>
<td>0.08</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>No. regions $m_s$ increased</td>
<td>−0.39</td>
<td>0.03</td>
</tr>
<tr>
<td>6MWD</td>
<td>No. regions $m_r$ increased</td>
<td>−0.13</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>No. regions $m_s$ increased</td>
<td>0.44</td>
<td>0.02</td>
</tr>
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**Figure 2.** Ventilation curves for each region in a representative patient. Note that the initial wash-in phase is followed by an equilibrium period and then by a two-component washout portion. The bottom two curves are regions where this patient’s emphysema was worse.
Relationship Between Ventilation Washout Parameters and Physiologic Outcome

The number of regions in which m_s increased correlated with various measures of airflow (FEV_1, FEF_{25-75%}, and FEF_{50%}), RV/TLC ratio, PaCO_2, and 6 MWD (Table 2). Figure 3 shows the relationship between the number of regions in which m_s increased per patient and FEV_1 (Fig 3, left, A) and RV/TLC ratio (Fig 3, right, B) post-LVRS. m_r showed no relationship with any physiologic parameters (Table 2).

Relationship Between m_r, m_s, and Physiologic Parameters and the Region of Resection

Of 174 total lung regions analyzed (6 regions in each of 29 patients), 82 regions (47%) were operated on. All patients had at least two regions operated on, and one patient had five regions operated on. The mean number of regions operated on was 2.8 ± 0.9.

In the 74 regions where m_s increased, the increases occurred regardless of whether or not the region was operated on, and the magnitude of the increase was no different between the regions that had been operated on and those that had not (p = 0.7). Similarly, in the 79 regions where there was an increase in m_r, the increase was irrespective of whether the region was operated on (Fig 4).

There was no relationship between the number of regions operated on and any physiologic parameter.

Effect of LVRS on Physiologic Parameters

Baseline and post-LVRS physiologic data are shown in Table 3. There were significant differences between the pre-LVRS and post LVRS values for forced vital capacity, FEV_1, RV/TLC ratio, FEF_{25-75%}, FEF_{50%}, PaCO_2, and 6MWD. There was no significant change in the ratio of PaO_2/fraction of inspired oxygen (FiO_2) ratio following LVRS.

Discussion

These data suggest that LVRS (1) produces an increase in m_s, reflecting improved small airways ventilation, which significantly correlates with physiologic parameters of airflow (FEV_1, FEF_{25-75%}, and FEF_{50%}), gas trapping (RV/TLC ratio), reduction in PaCO_2, and exercise (6 MWD), and (2) affects regional ventilation, independent of the area or extent of resection.

Airflow obstruction in emphysema is principally related to a loss in lung elastic recoil. The loss of elastic recoil is associated with decreased airflow. LVRS, by increasing elastic recoil, facilitates...
greater airway traction and support, thereby increasing airway caliber, thus improving airflow, all factors that presumably contribute to improved lung function and a reduction in dyspnea in patients undergoing this procedure.5

Airflow through the lung is principally characterized by two different properties. In the large conducting airways (trachea down to the terminal bronchiole), gas flow is convective. The flow is relatively rapid. At the level of the terminal bronchiole, as airways become smaller and give rise to alveoli, the flow pattern is markedly reduced, and gas transport occurs predominantly by molecular diffusion.8 This change in flow pattern at the level of the terminal bronchiole is related to the abrupt increase in cross-sectional area of the airways.

When we examined the washout phase of 133Xe during lung ventilation scanning, we found a biphasic pattern of gas washout. We hypothesized that this biphasic pattern initially reflects the gas emptying of the large airways (bulk flow or convective gas transport), followed by gas emptying from the smaller, more distal airways. When we apply this observation to examine specific regions of the lung, we can appreciate the relative differences in the degree of gas emptying, but, more precisely, we can distinguish the relative contribution of each type of gas flow in each particular region.

The retention of xenon in the lung is indicative of obstructive airways disease, and inhomogenous clearance of xenon from the lung is an indication of regional airways disease.2 Early washout images are related to the clearance of xenon from healthy airways, while later washout images show evidence of regions with prolonged time constants.2 Since small airways (ie, those <2 mm in diameter) are the major site of obstruction in emphysema,9 and since the time constant is therefore prolonged, the later portion of washout reflects these abnormal airways with prolonged time constants. Washout curves, particularly in patients with obstructive lung disease, are not monoexponential.2 Rather, the pattern of xenon clearance can best be described as a biexponential equation reflecting early, rapid washout from more normal (ie, larger) airways, and in the subsequent portion, delayed clearance from the small abnormal airways.

In emphysema, because of alveolar destruction, we expect the slow component of washout to be less. There is delayed lung emptying in emphysema in part due to a loss of elastic lung recoil. This delay in lung emptying is evident in the washout phase of the ventilation scan. When this washout component is examined quantitatively, the delay in emptying is particularly slow during the second exponential phase. This observation is consistent with the concept of small airways being affected in emphysema.

The reduction in PaCO2 and the nonsignificant change in the PaO2/FIO2 ratio that we observed following LVRS are consistent with the notion that there is a variable effect of LVRS on gas exchange based on the V/Q ratio of both the lung units resected and the units remaining.10 In our patients, a reduction in PaCO2 suggests that proportionately fewer high V/Q units remained following LVRS.

We conclude the following about LVRS: (1) that it globally enhances lung function, which is suggested by improved spirometry, lower PaCO2, and increased 6MWD; (2) that it improves ventilation through small airways; (3) that it is associated with an improvement in physiologic parameters that correlate with the enhancement in small airways function; and (4) that it improves regional ventilation in the lung independent of the area resected.

### References