Apical Perfusion Fraction as a Predictor of Short-term Functional Outcome Following Bilateral Lung Volume Reduction Surgery*

Robert M. Kotloff, MD, FCCP; John Hansen-Flaschen, MD, FCCP; David A. Lipson, MD; Gregory Tino, MD, FCCP; Selim M. Arcasoy, MD, FCCP; Abass Alavi, MD; and Larry R. Kaiser, MD, FCCP

Study objectives: To examine whether relative hypoperfusion to the apical one third of the lungs as determined by lung scintigraphy predicts a favorable functional outcome following bilateral lung volume reduction surgery (LVRS).

Methods: We performed a retrospective analysis of 128 patients who underwent bilateral LVRS. An apical perfusion fraction (AP%), defined as the percentage of total lung perfusion to the apical one third of both lungs, was derived for each patient by quantitative scintigraphy technique. Pulmonary function testing and 6-min walk test (6MWT) data were obtained preoperatively and 3 to 6 months postoperatively.

Results: The mean (± SD) improvement in FEV₁ was 309 ± 240 mL, 209 ± 293 mL, and 116 ± 224 mL for patients with an AP% of < 10%, 11 to 20%, and > 20%, respectively (p = 0.01, analysis of variance [ANOVA]). The likelihood of experiencing an increase in FEV₁ ≥ 200 mL was 68% for those with an AP% ≤ 10% but only 31% for those with an AP% > 20%. Preoperative and postoperative 6MWT data were available for 109 of 128 patients. Improvement was 250 ± 252 feet, 205 ± 299 feet, and 77 ± 200 feet for patients with AP% ≤ 10%, 11 to 20%, and > 20%, respectively (p = 0.04, ANOVA). While 50% of those with an AP% ≤ 10% improved their 6MWT by ≥ 180 feet, only 21% of those with an AP% > 20% did so.

Conclusion: This retrospective analysis suggests that quantification of apical perfusion by nuclear scintigraphy assists in predicting the likelihood of short-term functional improvement after LVRS.

Key words: COPD; emphysema; lung volume reduction surgery; perfusion scintigraphy

Abbreviations: ANOVA = analysis of variance; AP% = apical perfusion fraction; LVRS = lung volume reduction surgery; 6MWT = 6-min walk test; RV = residual volume

Lung volume reduction surgery (LVRS) is an evolving surgical technique for treatment of advanced emphysema. Significant short-term improvements in pulmonary function, exercise tolerance, dyspnea, and quality of life have been reported in multiple retrospective case series and in at least two prospective, randomized trials. However, the response to LVRS is not uniform. Twenty-five to 50% of patients undergoing the procedure do not appear to benefit. In order to optimize the clinical utility of this procedure, it is essential to identify preoperative characteristics predictive of a favorable functional response.

As initially conceived by Brantigan et al. and subsequently refined by Cooper et al., LVRS is deemed to be best suited for patients with heterogeneously distributed disease, with resection targeted at the most severely diseased portions of lung tissue. The rationale for this strategy is straightforward. The resected tissue is presumed to contribute little to overall lung function and gas exchange, and its loss should not, therefore, adversely impact the patient. As importantly, resection of nonfunctioning,
space-occupying tissue permits the expansion of remaining healthier tissue, thus enhancing the overall elastic recoil of the remaining lung.11

Preliminary data from several centers support the notion that patients with heterogeneously distributed and, in particular, apically predominant emphysema derive the greatest functional benefit from LVRS.4,12,13 Identification of such patients has relied on a number of radiographic techniques, including standard chest radiography,13,14 CT imaging,8,15–17 and lung perfusion scintigraphy.12,15 To date, however, these techniques have either employed quantitative analysis that is not widely available (ie, CT morphometry) or semiquantitative scoring systems that require an experienced reader and are subject to interobserver variability.

To address these potential shortcomings, we have devised a simple surrogate marker for apically predominant emphysema—derived from computer analysis of lung perfusion scintigraphy images—that we have called apical perfusion fraction (AP%). The purpose of this study was to determine the utility of the AP% in predicting short-term functional improvement following LVRS.

**Materials and Methods**

**Patient Population**

We performed a retrospective analysis of 183 consecutive patients who underwent bilateral LVRS via either median sternotomy or video-assisted thoracoscopic surgery at our institution between August 1993 and May 2000. Patients who underwent bullectomy for giant bullous disease and patients participating in the National Emphysema Treatment Trial were not included in this population. Of the 183 patients, 15 patients (8.2%) died within 6 months of surgery and consequently did not undergo postoperative functional assessment. Of the 168 survivors, 128 patients had a complete set of preoperative and postoperative pulmonary function studies and 109 of these patients had complete 6-min walk test (6MWT) data before and after surgery; these patient groups served as the populations for analysis in this study.

Patient selection criteria employed by our program have been previously published.1 Briefly, patients who underwent LVRS had evidence of severe airflow obstruction, were severely hyperinflated with a residual volume (RV) [by body plethysmography] > 200% of predicted, and had areas of hypoperfused lung by perfusion scintigraphy that could be targeted for resection. All patients selected for surgery were required to complete a 6-week course of preoperative pulmonary rehabilitation and a second 6-week course following surgery.

**Quantitative Perfusion Scintigraphy**

Prior to surgery, all patients underwent quantitative perfusion lung scintigraphy using standard techniques. Approximately 4 mCi of 99mTc-labeled macroaggregated albumin was IV administered to the supine patient; images were subsequently obtained in eight standard projections with the patient in an erect position. Since posterior views allow best overall estimates of pulmonary perfusion, we routinely used this projection for generation of quantitative perfusion data. The boundaries of the lungs were defined by enhancing the peripheral perfusion of the lungs (including the upper lung zones) by reducing the upper threshold for displaying the intensity of pixel count in the entire image set. The lung zones were defined by assigning two rectangles whose perimeters abutted on the outermost pixel in the superior, medial, inferior, and lateral boundaries of the lungs. Thereafter, the rectangles were equally divided into upper, middle, and lower zones by assigning two horizontal lines within each rectangle (Fig 1). The counts in each of the six lung zones were individually

<table>
<thead>
<tr>
<th>Left Lung</th>
<th>Right Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>252807.0</td>
<td>245852.2</td>
</tr>
<tr>
<td>50.7</td>
<td>49.3</td>
</tr>
<tr>
<td>9.1</td>
<td>11.0</td>
</tr>
<tr>
<td>21.5</td>
<td>21.1</td>
</tr>
<tr>
<td>20.0</td>
<td>17.2</td>
</tr>
</tbody>
</table>

**Figure 1.** Representative lung perfusion image, posterior view. A grid composed of six equal zones is superimposed on the lung image. The computer-derived percentage of total counts to each of the six regions (reflecting percentage of total perfusion) is shown to the right of the lung image. In this example, the AP% is 9.1% + 11.0% = 20.1%.

**Lung Distribution**
determined, and the percentage of perfusion to each lung zone was calculated by dividing the counts of the lung zone of interest by the total counts in both lungs, multiplied by 100. The AP% was calculated as the sum of the percentage of perfusion to the right and left upper lung zones (Fig 1).

Operative Approach

All patients underwent bilateral LVRS, with stapled resection of areas of lung deemed most severely diseased by preoperative perfusion scans and by intraoperative inspection. The procedure was performed by median sternotomy in 72 patients and by video-assisted thoracoscopic technique in 56 patients. We have previously demonstrated that the two procedures are associated with similar functional outcomes.1

Clinical Outcomes

For the purpose of this analysis, patients were classified into three groups based on preoperative AP%: ≤ 10%, 11 to 20%, and > 20%. The primary outcome measures were the change in FEV₁ and 6MWT distance at 3 to 6 months after LVRS, reflecting changes in the degree of airflow obstruction and exercise tolerance, respectively. In addition to examining the absolute magnitude of change in these parameters, we determined the percentage of patients in each AP% group who derived a “clinically significant benefit,” which we defined as an increase of ≥ 200 mL (and 12%) in the FEV₁, or ≥ 180 feet in the 6MWT distance. These thresholds are based on standards previously established in the literature.18,19

Statistical Analysis

StatView statistical program (version 5.0 for Windows; SAS Institute; Cary, NC) was used for statistical analysis. Data are expressed as mean ± SD. Analysis of variance (ANOVA), followed (when significant) by the Fisher’s Protected Least Significant Difference post hoc test, was used to compare differences in continuous variables among the three AP% groups. χ² analysis was employed to examine differences in categorical variables. A p value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the 128 patients comprising the study population are shown in Table 1. Reflecting our selection criteria, the population was characterized by severe airflow obstruction (mean FEV₁, 0.72 L; 26% predicted) and marked hyperinflation (mean RV, 5.05 L; 253% predicted). The distribution of patients among the three AP% groups was as follows: 34 of the patients (26.6%) had an AP% ≤ 10%, 59 patients (46.1%) had an AP% from 11 to 20%, and 35 patients (27.3%) had an AP% > 20%. There was no significant difference in baseline characteristics among the three groups (Table 1). Since not all of the preoperative arterial blood gas values were obtained with patients breathing room air, data on preoperative PO₂ were not included. Following LVRS, the mean improvement in FEV₁ for the entire group of 128 patients was 210 ± 270 mL. The association between AP% and change in FEV₁ is shown in Figure 2. Patients with an AP% ≤ 10% realized an improvement in FEV₁ of 309 ± 240 mL, those with a score of 11 to 20% improved by 209 ± 293 mL, and those patients with an AP% > 20% improved by a mean of 116 ± 224 mL (p = 0.01, ANOVA). To further investigate the utility of the AP% in predicting response to LVRS, we identified the percentage of patients in each group that achieved a “clinically meaningful” improvement in FEV₁. This was defined as an increase in FEV₁ of > 200 mL (in all cases, this was also > 12% of baseline value). As shown in Table 2, a favorable response was achieved by 68% of patients with an AP% ≤ 10%, 47% of those with a score of 11 to 20%, and only 31% of those with a score > 20% (p = 0.01).

One hundred nine of the 128 patients had complete preoperative and postoperative 6MWT data available for analysis. The mean improvement in 6MWT distance for this group was 186 ± 269 feet. When analyzed by AP% (Fig 3), the mean improvements in 6MWT distance were 250 ± 252 feet, 205 ± 290 feet, and 77 ± 200 feet for patients with AP% ≤ 10%, 11 to 20%, and > 20%, respectively (p = 0.04, ANOVA). Defining a clinically meaning-

Table 1—Preoperative Characteristics of the Study Group According to AP% Category*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (n = 128)</th>
<th>≤ 10% (n = 34)</th>
<th>11 to 20% (n = 59)</th>
<th>&gt; 20% (n = 35)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>60 ± 8</td>
<td>59 ± 6</td>
<td>61 ± 8</td>
<td>62 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>45</td>
<td>35</td>
<td>46</td>
<td>49</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>0.72 ± 0.25</td>
<td>0.68 ± 0.24</td>
<td>0.74 ± 0.26</td>
<td>0.72 ± 0.24</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>26 ± 7</td>
<td>25 ± 7</td>
<td>27 ± 7</td>
<td>26 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>FVC, L</td>
<td>2.25 ± 0.71</td>
<td>2.16 ± 0.69</td>
<td>2.32 ± 0.70</td>
<td>2.20 ± 0.74</td>
<td>NS</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>65 ± 13</td>
<td>64 ± 12</td>
<td>66 ± 13</td>
<td>63 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>RV, L</td>
<td>5.05 ± 1.27</td>
<td>5.10 ± 1.11</td>
<td>4.90 ± 1.18</td>
<td>5.26 ± 1.35</td>
<td>NS</td>
</tr>
<tr>
<td>RV, % predicted</td>
<td>253 ± 58</td>
<td>262 ± 54</td>
<td>247 ± 51</td>
<td>255 ± 74</td>
<td>NS</td>
</tr>
<tr>
<td>6MWT distance, feet</td>
<td>1,038 ± 303</td>
<td>1,034 ± 319</td>
<td>1,020 ± 311</td>
<td>1,072 ± 286</td>
<td>NS</td>
</tr>
<tr>
<td>PO₂, mm Hg</td>
<td>40 ± 5</td>
<td>41 ± 4</td>
<td>39 ± 5</td>
<td>42 ± 6</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated. NS = not significant.
†Comparison of the three AP% groups by ANOVA for continuous variables and χ² for categorical variables.
ful response as an increase in walk distance of > 180 feet, 50% of those with an AP% ≤ 10%, 43% of those with an AP% from 11 to 20%, and 21% of those with an AP% > 20% realized a favorable outcome (Table 2; p = 0.05).

**DISCUSSION**

Experience with LVRS accrued to date suggests that some highly select patients with advanced emphysema may derive at least short-term benefit in parameters of lung function and exercise tolerance. However, as many as 25 to 50% of surviving patients fail to demonstrate such improvement. The observed nonuniformity of response and the significant morbidity and mortality associated with LVRS have provided an impetus to search for preoperative predictors that would permit more selective application of the procedure. In the current study, we have demonstrated that a simple quantitative assessment of apical perfusion by standard lung scintigraphy, the AP%, is helpful in predicting short-term functional outcomes. Specifically, patients with marked apical hypoperfusion as indicated by an AP% ≤ 10% achieved a greater degree of improvement in FEV₁ and 6MWT distance than those who had better relative perfusion to the apices.

The notion that topographic heterogeneity of emphysema is critically important to the success of LVRS dates back to the original description of the procedure by Brantigan et al., who emphasized the importance of targeting the most severely diseased and presumably functionless areas of lung while leaving behind healthier tissue whose function could be enhanced by providing room for expansion within the thorax. The requirement for heterogeneity of emphysema distribution was adopted by Cooper et al. in their resurrection of LVRS in the early 1990s. The subsequent incorporation of this requirement into standard selection criteria utilized by a majority of centers preceded any scientific verification of its validity and any standardization of its measurement.

Utilizing quantitative perfusion scintigraphy, we have chosen to assess heterogeneity in a functional rather than anatomic fashion by assessing regional variations in blood flow within the lung. The presumption in using this approach in patients with advanced emphysema is that areas of relative hypoperfusion correspond to geographic regions that are most severely diseased. Quantitative perfusion scintigraphy has a number of features that make it an attractive method of assessing LVRS candidates: it is widely available, requires no breath-holding or patient effort, and provides a digital output that is readily amenable to quantitative analysis. We devised a simple, objective, computer-generated index of apical perfusion, the AP%, representing the percentage of total perfusion that is directed to the upper one third of both lungs. The requirement for heterogeneity in disease distribution would be reflected in a low AP%. In contrast, a high AP% provides less information about disease heterogeneity and distribution, since it could result either from homogeneously distributed disease (with rela-

**Table 2—Response Rate According to AP% Category**

<table>
<thead>
<tr>
<th>Variables</th>
<th>≤ 10%</th>
<th>11 to 20%</th>
<th>&gt; 20%</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ responders,*</td>
<td>68</td>
<td>47</td>
<td>31</td>
<td>0.01</td>
</tr>
<tr>
<td>% of total group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWT responders,†</td>
<td>50</td>
<td>43</td>
<td>21</td>
<td>0.05</td>
</tr>
<tr>
<td>% of total group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patients achieving an improvement in FEV₁ ≥ 200 mL and ≥ 12%.
†Patients achieving an improvement in 6MWT distance ≥ 180 feet.
tively even perfusion to all lung zones) or from focal regions of severe disease in the middle or lower lung zones.

Our finding that lung scintigraphy provides meaningful predictive information with respect to functional outcomes is in agreement with previous studies. Wang and colleagues studied 96 patients and utilized a semiquantitative scoring of scintigraphy patterns. Similar to our results, they found that the greatest degree of improvement in FEV	extsubscript{1} occurred in association with upper-lung-zone-predominant disease. In a study of 70 patients, Thurnheer and colleagues utilized a visual analysis that categorized perfusion scan patterns into markedly heterogeneous, intermediately heterogeneous, and homogeneous categories. The magnitude of improvement in FEV	extsubscript{1} was 57 ± 8%, 38 ± 9%, and 23 ± 9% for the markedly heterogeneous, intermediately heterogeneous, and homogeneous categories, respectively, although the differences among the three groups were not statistically significant and the correlation with outcomes was not as strong as with CT scoring. In contrast to our quantitative, computer-generated technique of scoring the scintigraphy scans, these two studies relied on observer-generated assessment.

This not only mandates the involvement of highly experienced interpreters but also introduces the problem of interobserver variability. For example, in the study by Thurnheer et al., there was agreement among at least five of the six observers in only 55% of studies. Using an apical perfusion score similar to ours in a preliminary study of 20 patients, Oey and colleagues reported a significant correlation between this score and postoperative functional and health-status outcomes.

Other investigators, employing morphologic rather than functional measures of emphysema severity and distribution, have drawn conclusions similar to our own. Utilizing sophisticated visual scoring systems of chest radiographs, two groups demonstrated that the degree of heterogeneity and, in particular, an upper-lobe-predominant distribution pattern of emphysema, were associated with a more favorable improvement in FEV	extsubscript{1} and 6MWT distance. Similar results were noted by others with the use of semiquantitative scoring of CT scans and quantitative CT morphometry. The information derived from functional and anatomic imaging may prove to be complementary rather than redundant. In a direct comparison of perfusion scintigraphy and CT imaging, Thurnheer and coworkers observed heterogeneity of perfusion in 16 of 22 patients with ostensibly homogeneous disease as assessed by CT scoring. This suggests that scintigraphy may be more sensitive than visual assessment of CT images in detecting subtle differences in regional distribution of disease. Conversely, CT offers several potential advantages over scintigraphy. CT imaging permits confirmation that poorly perfused areas identified by scintigraphy are, in fact, a result of emphysematous destruction of the involved region of lung. This is critically important in light of evidence that LVRS is suited only for patients whose airflow obstruction is due to emphysema and not to those whose disease is intrinsic to the airways. CT scans also permit identification of other pulmonary processes, such as lung nodules, bronchiectasis, or chronic infection, which would influence the suitability of the patient for LVRS or direct the targeted resection of abnormal areas.

While we have demonstrated a correlation between AP% and functional outcome, the limitations of this score in selection of patients must be acknowledged. One-third of patients with an AP% ≤ 10% failed to realize an improvement in FEV	extsubscript{1} of ≥ 200 mL and one half of patients failed to increase their 6MWT distance by ≥ 200 feet. Conversely, nearly a third of patients with an AP% > 20% did experience such an improvement in FEV	extsubscript{1} and one fifth of patients achieved a clinically significant improvement in 6MWT distance. Assessment of heterogene-

Figure 3. Scatter plot depicting the change in 6MWT distance at 3 to 6 months after LVRS for patients within each of the three AP% groups. The short horizontal bars depict the mean value for each group; p = 0.04 (ANOVA) for comparison among the three groups; post hoc paired comparisons achieving statistical significance are shown.
ity by chest radiography and CT imaging have yielded similarly crude correlations with functional outcomes, suggesting that the imprecise predictive value of the AP% is not due to limitations inherent in the use of perfusion scintigraphy. It is likely that heterogeneity is only one of several factors critical to the outcome of LVRS. In addition to augmenting elastic recoil of the remaining lung, LVRS may also effect improvement by reducing the degree of hyperinflation, allowing the diaphragm to ascend to a more mechanically favorable position. Thus, factors such as the degree of preoperative hyperinflation and the volume of tissue removed may also dictate the magnitude of functional improvement. An additional potential limitation of the apical perfusion fraction is that it cannot identify patients with markedly heterogeneous but basilar predominant disease, a condition encountered in patients with α₁-antitrypsin deficiency as well as in some without this condition. In our series, there was an insufficient number of patients with basilar hypoperfusion (ie, ≤10% total perfusion to the lower thirds) to allow analysis of their response to LVRS. However, observations by multiple other investigators have suggested that functional outcomes in this group of patients are inferior to those achieved in patients with apically distributed disease, although there is at least one study suggesting equivalent outcomes. Additional experience is required to settle this issue; certainly the quantitative scoring system we have proposed could be easily adapted to detect basilar predominant disease if this distinction proves to be critical.

Finally, the incomplete nature of our database must be acknowledged as a potential limitation. Fifteen patients died within the first 6 months postoperatively and were excluded from our analysis. Including these patients as “nonresponders” would not have significantly altered the predictive utility of the AP% (Table 2). Analyzed in this fashion, the percentage of patients deriving a clinically meaningful improvement in FEV₁ would have been 59% (vs 68%), 47% (vs 47%), and 25% (vs 31%) for the ≤10% AP%, 11 to 20% AP%, and >20% AP% groups, respectively. Similarly, the percentage of patients deriving a clinically meaningful improvement in 6MWT distance would have been 42% (vs 50%), 40% (vs 41%), and 16% (vs 21%) for the ≤10% AP%, 11 to 20% AP%, and >20% AP% groups, respectively. There was also incomplete follow-up of survivors; one fourth of survivors did not undergo pulmonary function testing within the initial 6 months, and one third of patients did not undergo follow-up 6MWTs in this time frame. Since relatively equal proportions of patients were lacking follow-up data in each AP% group, any bias introduced by the incomplete data should be minimized. We did not report data beyond the initial 6 months because our intent was not to examine the durability of response but only the magnitude of response to LVRS. Numerous studies have confirmed that peak functional effects occur by 6 months following surgery, justifying our selection of this time point.

In conclusion, we have developed a simple, quantitative index of apical perfusion derived by lung scintigraphy that assists in predicting the likelihood of short-term functional response to LVRS. Further study is needed to verify and refine the approach described herein and to compare it to other imaging modalities. Derivation of receiver operating characteristic curves from a larger, prospectively acquired database will be necessary to determine the most appropriate cutoff values for AP% that would optimize the predictive value of the index. Additionally, more information is needed on the relationship between zones of hypoperfusion assessed by scintigraphy and zones of emphysema assessed by CT imaging. The ongoing National Emphysema Treatment Trial has incorporated quantitative perfusion scintigraphy and CT imaging in the evaluation of all participants and should provide an unprecedented opportunity to study the merits of preoperative imaging in the selection of candidates for LVRS.

ACKNOWLEDGMENT: The authors gratefully acknowledge Jeffrey Edelman, MD; Harold Falesky, MD; Joseph Bavaria, MD; Joseph Friedberg, MD; Joseph Shrager, MD; Jim Mendez, MSN; and Mary Louise Gerahty, BSN for contributions to patient care. We are also grateful to Peter Wahl and Theresa Alcorn for assistance with the database.

REFERENCES