Semi-quantitative ventilation/perfusion scintigraphy and single-photon emission tomography for evaluation of lung volume reduction surgery candidates: description and prediction of clinical outcome

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Abstract. Ventilation/perfusion scans with single-photon emission tomography (SPET) were reviewed to determine their usefulness in the evaluation of lung volume reduction surgery (LVRS) candidates, and as a predictor of outcome after surgery. Fifty consecutive planar ventilation (^{99m}Tc-DTPA aerosol) and perfusion (^{99m}Tc-MAA) scans with perfusion SPET of patients evaluated for LVRS were retrospectively reviewed. Technical quality and the severity and extent of radiotracer defects in the upper and lower halves of the lungs were scored from visual inspection of planar scans and SPET data separately. An emphysema index (EI) (extent × severity) for the upper and lower halves of the lung, and an EI ratio for upper to lower lung were calculated for both planar and SPET scans. The ratios were compared with post-LVRS outcomes, 3, 6 and 12 months after surgery. All perfusion and SPET images were technically adequate. Forty-six percent of ventilation scans were not technically adequate due to central airway tracer deposition. Severity, extent, EI scores and EI ratios between perfusion and SPET were in good agreement ($r = 0.52$–0.68). The mean perfusion EI ratio was significantly different between the 30 patients undergoing bi-apical LVRS and the 17 patients excluded from LVRS (3.3 ± 1.8 versus 1.2 ± 0.7; $P < 0.0001$), in keeping with the anatomic distribution of emphysema by which patients were selected for surgery by computed tomography (CT). The perfusion EI ratio correlated moderately with the change in FEV_1 at 3 months ($r = 0.37$, $P = 0.04$), 6 months ($r = 0.36$, $P = 0.05$), and 12 months ($r = 0.42$, $P = 0.03$), and the transition dyspnea index at 6 months ($r = 0.48$, $P = 0.014$) after LVRS. It is concluded that patients selected to undergo LVRS have more severe and extensive apical perfusion deficits than patients not selected for LVRS, based on CT determination. SPET after aerosol V/Q imaging does not add significantly to planar perfusion scans. Aerosol DTPA ventilation scans are not consistently useful. Perfusion lung scanning may be useful in selecting patients with successful outcomes after LVRS.

Key words: Emphysema – V/Q scintigraphy – Single-photon emission tomography – Lung volume reduction surgery

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Introduction

Emphysema is a chronic progressive lung disease affecting approximately 2 million people in the United States [1]. Although the incidence of emphysema in women is rising, it is more common in men [2], and is associated with smoking [3]. Medical treatment is supportive and includes corticosteroids, bronchodilators, pulmonary rehabilitation, supplemental oxygen and cessation of smoking [4]. In general, severe emphysema is a progressive disease and medical treatment is symptomatic and supportive, with most patients eventually ending up on a lung transplant list. Lung transplantation, however, although of proven therapeutic utility, is not widely available to benefit the majority of patients requiring treatment [5]. In addition, following transplantation there is significant morbidity and mortality secondary to long-term immunosuppressive therapy and chronic allograft rejection, otherwise known as obliterative bronchiolitis [6, 7]. Lung volume reduction surgery (LVRS) is a technique being evaluated for the management of patients with severe emphysema.

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Patients with emphysema that is upper lobe predominant, with relatively preserved lower lung parenchyma as evaluated by computed tomography, have a better outcome after LVRS than patients with more diffuse disease [8–10]. We reviewed planar ventilation/perfusion (V/Q) scintigraphy and single-photon emission tomography (SPET) images of a consecutive patient cohort evaluated for LVRS in order to determine: (1) whether SPET added additional information regarding the size and extent of perfusion defects to that obtained from planar imaging, (2) whether ventilation scans were useful in patient assessment, despite the frequent central airway radiotracer deposition in obstructive lung disease, and (3) whether the visual assessment of perfusion scan defects correlated with clinical improvement after LVRS, particularly the improvement in forced expiratory volume in 1 s (FEV_1), the 6-min walk distance [11], and the transition dyspnea index (TDI) [12, 13].

Materials and methods

Patient population

All consecutive V/Q scintigrams with SPET performed between June and November 1995 in the evaluation of candidates for LVRS were retrospectively reviewed in a blinded manner. Patients were divided into two categories: (1) patients who underwent surgery, and (2) patients who were not judged eligible for surgery. Computed tomography (CT) of the lungs was routinely obtained during initial evaluation, at which time each patient was reviewed at the multi-disciplinary weekly LVRS program conference attended by pulmonologists, a thoracic surgeon, a thoracic radiologist and a clinical coordinator. Studies reviewed included history and physical examination, functional and physiologic testing, chest radiography and computed tomography. Patients who were considered eligible had additional studies, which included V/Q scintigraphy with SPET, and underwent a 6-week pulmonary rehabilitation program. The final decision for surgery was made mainly on the basis of CT imaging and functional and physiologic testing, with V/Q scintigraphy and SPET playing a lesser role. This study was approved by our institutional review board and informed consent was obtained from all patients.

Scintigraphic technique

Ventilation scans followed the inhalation of technetium-99m diethylene triamine penta-acetic acid (DTPA) aerosol from a 50-mCi reservoir where 1–2 mCi was inhaled (the Ultravent System, Mallinckrodt Medical, St. Louis, Mo.). Planar perfusion scans were performed after ventilation and followed an intravenous injection of 5 mCi of ^{99m}Tc-macroaggregated albumin (mAA) to achieve a count rate of 3–5 times that for ventilation. A Siemens Dual Head Multispect II camera was used for all nuclear imaging. Posterior, anterior, right and left lateral and four oblique views (RAO, LAO, RPO and LPO) were obtained. SPET images were obtained with a dual-head scanner with 32 projections per head, a 64×64 matrix and 25 s/imaging stop, utilizing a low-energy, high-resolution collimator. Planar scans consisted of posterior, anterior, right and left lateral and four oblique images.

Qualitative scoring

All planar ventilation scans, planar perfusion scans and SPET studies were reviewed by a consensus panel of three readers over a period of several weeks. These images were viewed for the extent and severity of perfusion and ventilation abnormalities. Reviewers were blinded to the patient's name, decision regarding surgery and surgical findings. Disagreements between the three reviewers were resolved by further discussion, and if agreement was still not reached, by a vote.

Each ventilation, perfusion and SPET study was initially categorized as technically adequate or not technically adequate. Each lung of the technically adequate studies was divided into an upper and a lower zone by a line midway between the lung apex and the dome of the diaphragm, for a total of four zones for each ventilation, perfusion and SPET scan. Both upper and lower zones of both lungs were assessed and scored separately for each planar ventilation and perfusion scan from the analog images. The SPET images were interactively reviewed without the planar image data on a computer monitor with the ability to rotate the images 360° and to obtain tomographic slices in axial, coronal, and sagittal planes. SPET interpretations were rendered by consensus during a reading session approximately 1 month after the scoring of the planar images.

For both planar perfusion and SPET images, the overall size of scintigraphic defects was qualitatively graded as a percentage with respect to the percent volume of abnormal lung perfusion within each zone. The severity (degree of absent radiotracer) was then classified for each zone as normal, mild, moderate or severe. The qualitative assessment of defect severity was assigned a numerical weighting factor for statistical analysis as follows: normal = 1, mild = 2, moderate = 3, severe = 4. An emphysema index (EI) was then calculated for each upper and lower zone by the product of disease extent (%) and qualitative severity. Finally, a semiquantitative EI ratio of upper lung to lower lung was calculated from the sum of the right upper and left upper zone EI divided by the sum of the right lower and left lower zone EI.

Outcome measures

Pulmonary function tests (PFTs). PFTs were performed on a single day after administration of 2.5 mg of inhaled albuterol via nebulizer. Spirometric studies ($FEV_{1)}$ were performed on a calibrated pneumotachograph (Medical Graphics Co.); best overall effort was chosen and values were expressed relative to standards of Morris [14].

Transition dyspnea index (TDI). The TDI was administered using the methodology described by Mahler et al. [13]. The TDI is a measure of the change in dyspnea from a baseline state, in which patients indicate their change in functional impairment, task magnitude and task effort, each by a score of –3 to +3 (major deterioration to major improvement). The three scores are summed, with the final score ranging from –9 to +9. The lower the TDI score, the greater the deterioration or increase in dyspnea. The higher the TDI score, the greater the improvement in dyspnea.

Six-minute walk test (6MWT). The 6MWT was performed using the methodology described by Guyatt et al. [11]. Patients were encouraged to walk as far as they were capable of in 6 min in a level, pre-measured hallway. Patients were allowed to rest during the test. A nurse specializing in pulmonary medicine administered the test. Supplemental oxygen was administered to maintain peripher-

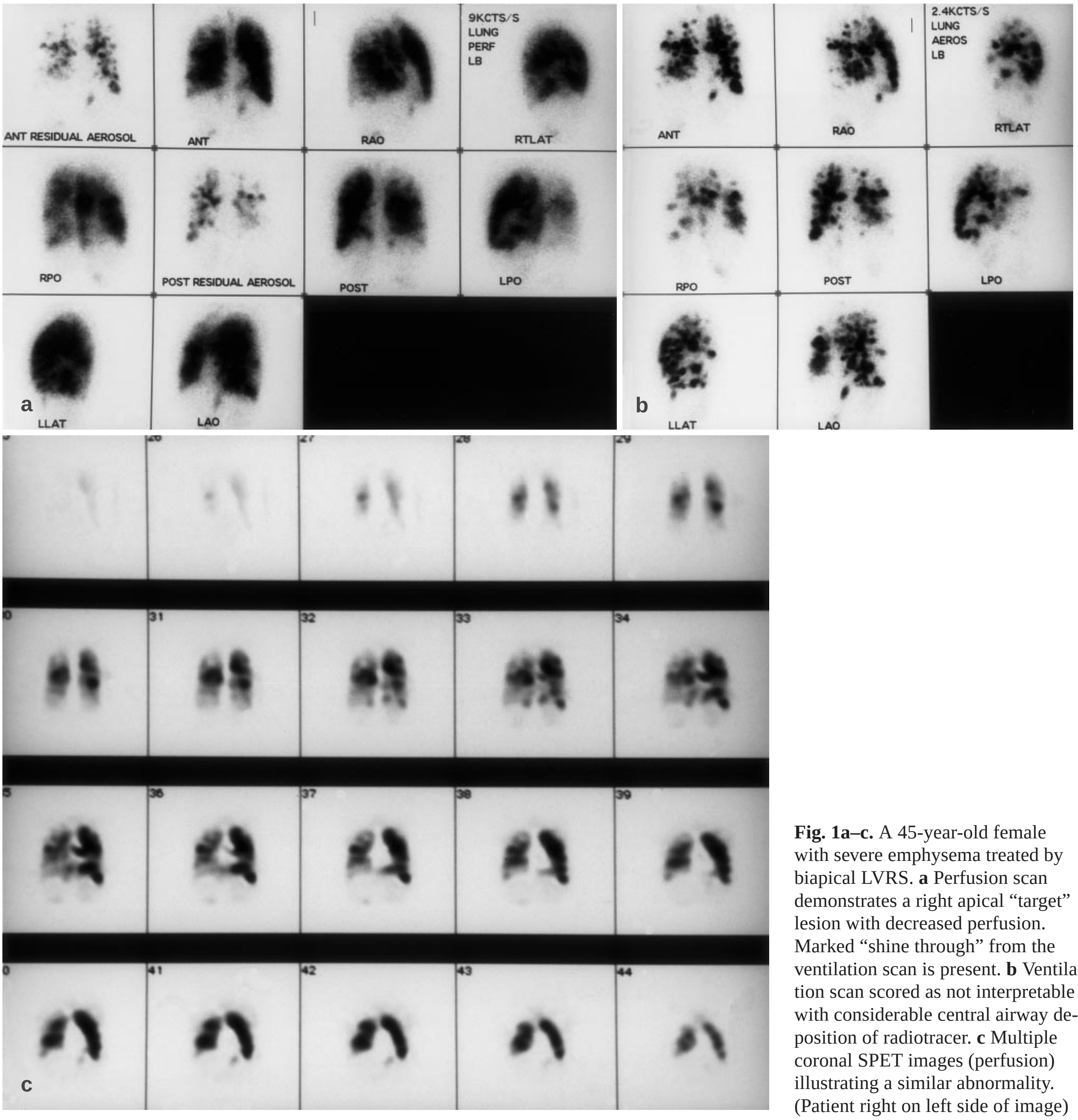

Fig. 1a–c. A 45-year-old female with severe emphysema treated by biapical LVRS. **a** Perfusion scan demonstrates a right apical "target" lesion with decreased perfusion. Marked "shine through" from the ventilation scan is present. **b** Ventilation scan scored as not interpretable with considerable central airway deposition of radiotracer. **c** Multiple coronal SPET images (perfusion) illustrating a similar abnormality. (Patient right on left side of image)

al arterial oxygen saturation at greater than or equal to 86%. The distance covered was recorded in feet.

Statistical analysis

Using the Pearson correlation coefficient, the EI ratios from planar perfusion scans scores and SPET scores were compared to determine whether the semi-quantitative assessment of SPET images yielded additional information relative to the planar perfusion data. EI ratios were compared between the group of 30 patients undergoing biapical LVRS and the 17 patients with diffuse disease denied surgery using a Student's *t* test. EI ratios were compared with the percent change in FEV_1 in liters, change in 6-min walk distance in feet, and the TDI, all at 3, 6 and 12 months following LVRS using simple linear regression and analysis of variance.

In addition to the above analysis, EI ratios were calculated for individual lungs (EI right upper lung/EI right lower lung; EI left upper lung/EI left lower lung) to determine whether the distribution of perfusion defects was generally symmetric or asymmetric between the two lungs.

Results

Fifty-five consecutive planar V/Q scans with SPET were reviewed. Five patients were not judged eligible for surgery for medical conditions including death, necrotizing

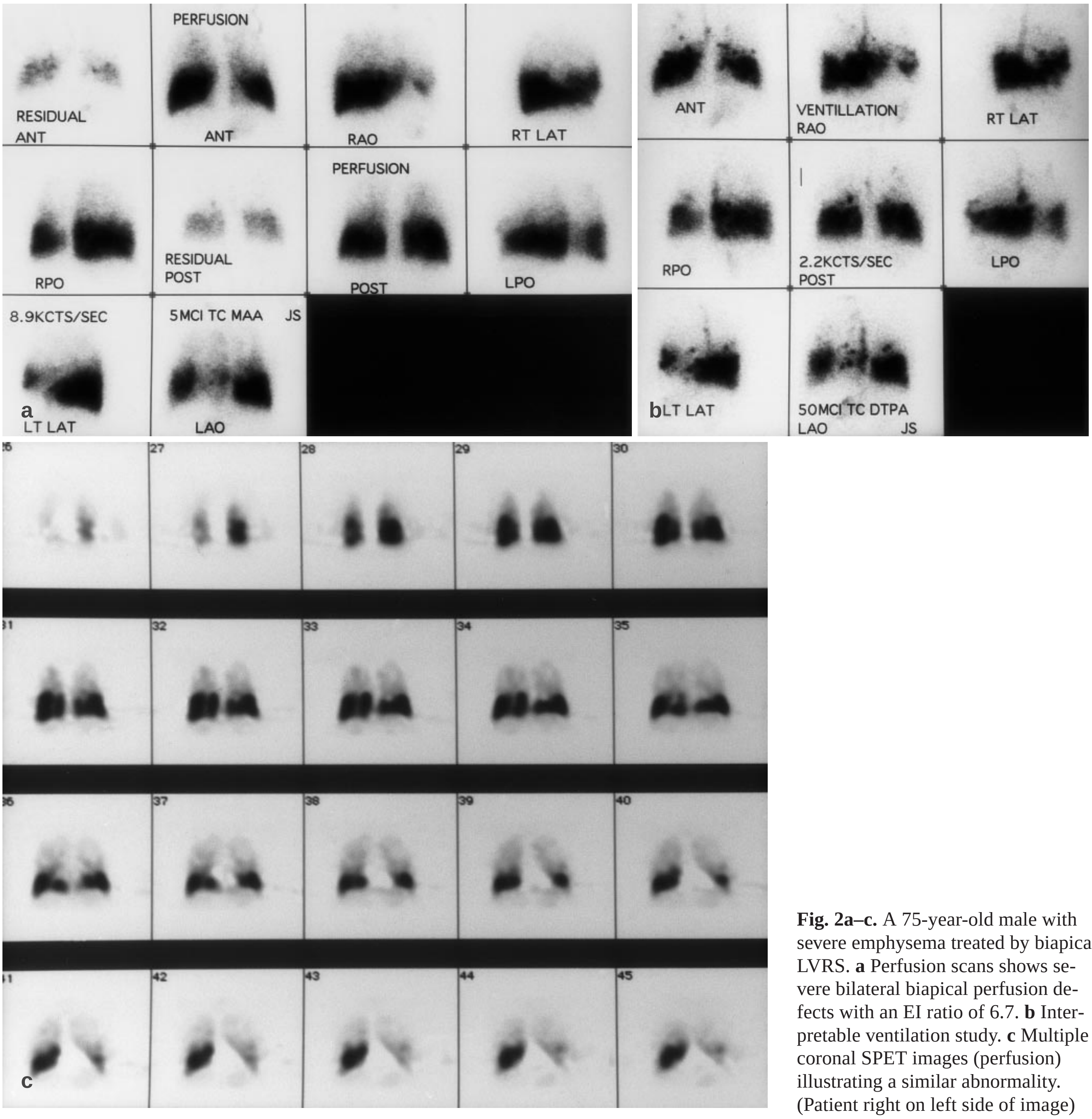

Fig. 2a–c. A 75-year-old male with severe emphysema treated by biapical LVRS. **a** Perfusion scans shows severe bilateral biapical perfusion defects with an EI ratio of 6.7. **b** Interpretable ventilation study. **c** Multiple coronal SPET images (perfusion) illustrating a similar abnormality. (Patient right on left side of image)

pneumonia, severe pulmonary hypertension, critical coronary artery disease with cor pulmonale, and a superimposed restrictive lung disease (asbestosis), and were excluded from further analysis. The remaining 50 patients form the study group. These 26 male and 24 female patients ranged in age from 45 to 75 years (mean = 64.3±8.9). Patients undergoing LVRS had either a median sternotomy for biapical reduction surgery (*n* = 30), or thoracotomy for unilateral apical (*n* = (2) or basal (*n* = 1) reduction surgery. The three patients having thoracotomy for unilateral apical or basal LVRS were excluded from further analysis. Seventeen patients were denied surgery by the multidisciplinary LVRS program team for diffuse disease.

Clinical outcomes for the 30 patients undergoing biapical LVRS are detailed in Table 1. There was a statistically significant increase in the mean FEV_1 and 6-min walk distance of the patients undergoing LVRS, between baseline and 3, 6 and 12 months after surgery. The mean increase in TDI was 5.5, 6.0 and 7.3, indicating at the same time points a considerable reduction in dyspnea.

Due to central airway tracer deposition, 46% (23/50) of ventilation scans were not assessed to be technically adequate for our analysis (Fig. 1. Therefore, further as-

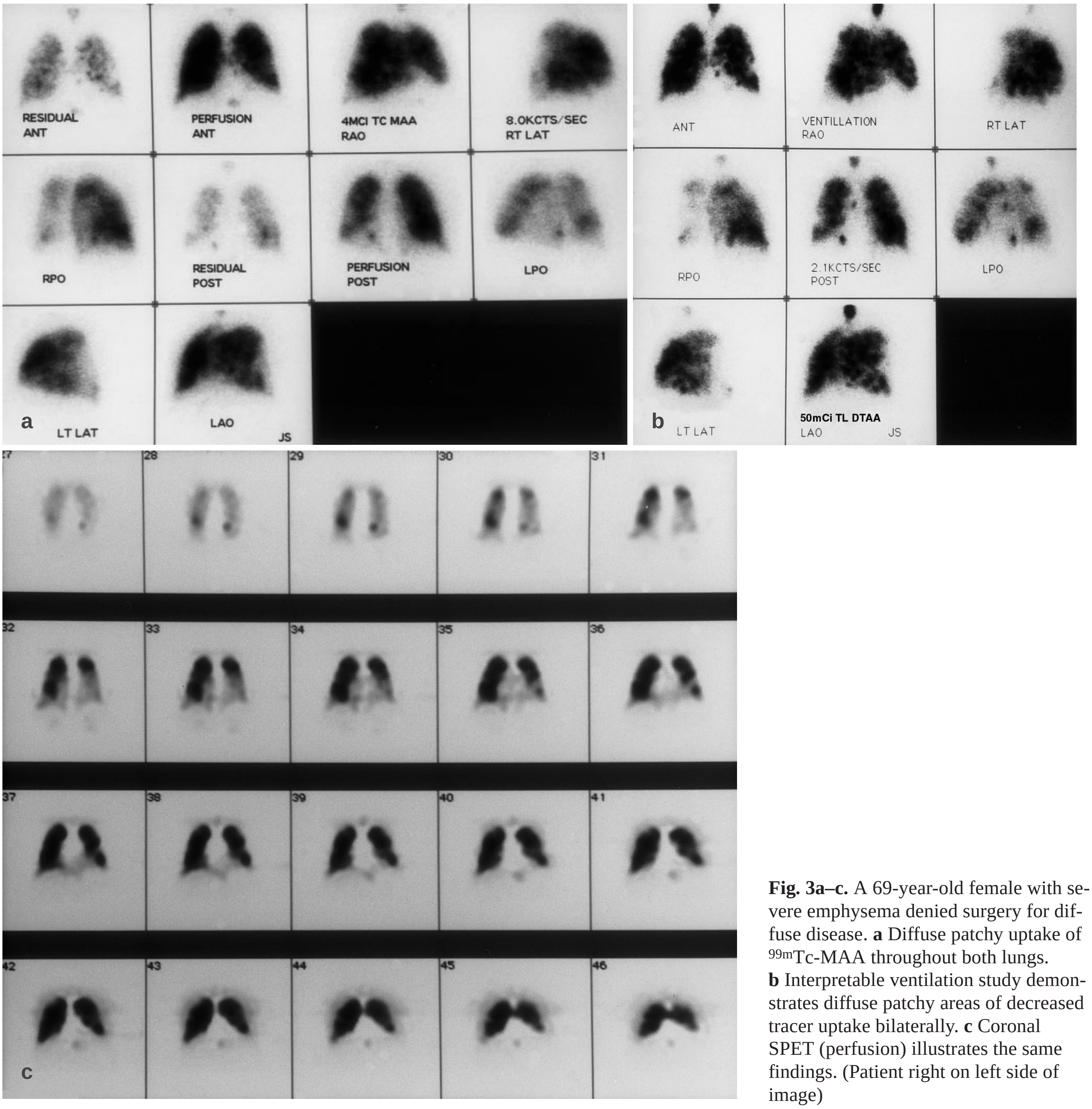

Fig. 3a–c. A 69-year-old female with severe emphysema denied surgery for diffuse disease. **a** Diffuse patchy uptake of ^{99m}Tc-MAA throughout both lungs. **b** Interpretable ventilation study demonstrates diffuse patchy areas of decreased tracer uptake bilaterally. **c** Coronal SPET (perfusion) illustrates the same findings. (Patient right on left side of image)

Table 1. Clinical outcome measure 3, 6, and 12 months after biapical LVRS

	Baseline (mean±SD)	3 months (mean±SD)	6 months (mean±SD)	12 months (mean±SD)
FEV$_1$ (l)*	0.71±0.99	0.99±0.37 (*n* = 30)	0.98±0.34 (*n* = 29)	0.96±0.36 (*n* = 24)
TDI**	–	5.5±4.0 (*n* = 28)	6.0±3.2 (*n* = 24)	7.3±2.4 (*n* = 17)
6MWT (feet)***	607±353	923±290 (*n* = 16)	1048±314 (*n* = 18)	1324±446 (*n* = 1(2)

SD, Standard deviation
* *P*<0.001 for baseline vs. 3, 6 and 12 months after LVRS; *t* test
** TDI, transition dyspnea index
*** 6MWT, 6 min walk test; *P* = 0.002 for baseline vs 3 months; *P* = <0.001 for baseline vs 6 and 12 months; *t* test

Table 2. Comparison of the EI of the upper and lower lungs in patients having LVRS and those denied surgery

	Mean	SD	Range	95% CI
LVRS group				
EI upper	308.7	137	90–850	295–321
EI lower	129.2	87.5	40–500	126–132
Patients denied LVRS				
EI upper	173.8	78.5	70–360	169–178
EI lower	179.1	63.6	100–325	175–182

SD, standard deviation; CI, confidence interval

Table 3. Correlation of perfusion scan EI ratio with clinical outcomes after bilateral LVRS

	% Change FEV_1 (*l*)		TDI		6MWT (feet)	
	r	*P*	*r*	*P*	*r*	*P*
3 Months	0.37	0.043	0.28	0.14	0.18	0.49
6 Months	0.36	0.052	0.48	0.014	0.25	0.22
12 Months	0.42	0.034	0.22	0.45	0.24	0.28

TDI, Transition dyspnea index; 6MWT, 6-minute walk test

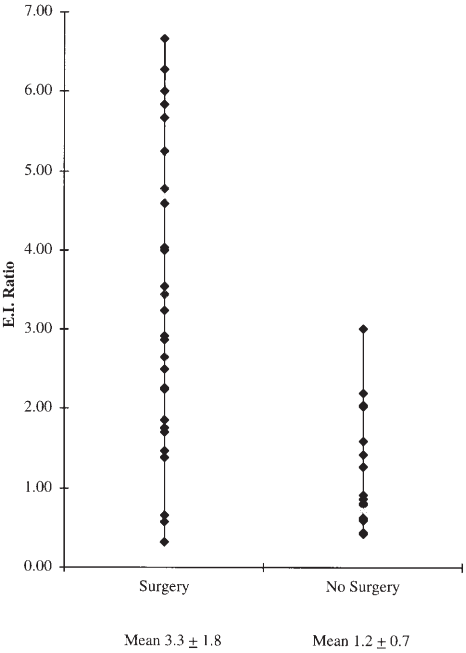

Fig. 4. EI ratio in 30 patients undergoing biapical LVRS and 17 patients denied LVRS. EI ratios in patients with LVRS are significantly higher than those in the non-LVRS group (Student's *t* test: $P<0.0001$)

sessment with EI ratios was not performed on ventilation image data. All perfusion and SPET scans were technically adequate.

Perfusion and SPET scan scores were in moderate-to-good agreement for both the size ($r = 0.56$) and severity ($r = 0.52$) of radiotracer defects, for the emphysema indices ($r = 0.68$), and for the EI ratios ($r = 0.54$).

The following is an analysis of EI ratios between the surgical and non-surgical groups, with LVRS outcome measures described for the planar perfusion scan scores only. Of the 30 patients undergoing bilateral apical LVRS, 22 patients had bilateral apical perfusion defects on perfusion scintigraphy (Fig. 2), four patients had unilateral apical perfusion defects, one patient had bibasilar defects, one patient had a unilateral basilar defect, and two patients had diffuse perfusion defects. Of the 17 patients denied surgery for diffuse disease (Fig. 3), ten patients had bilateral diffuse perfusion defects, consistent with diffuse emphysema. Three patients had diffuse perfusion defects in one lung with either apical or basal defects in the other lung, three patients had biapical perfusion defects, and one patient bibasilar perfusion defects. Table 2 compares the EI of upper and lower lungs in patients who had and those who were denied LVRS.

The mean perfusion EI ratio for the 30 patients undergoing bilateral apical LVRS was 3.3±1.8 (range 0.33–6.7; 95% C.I.), compared to 1.2±0.7 (range 0.42–3.0; 95% C.I.) for the 17 patients excluded from apical surgery for diffuse disease on CT scans (Fig. 4). Although not included in our analysis, it is of note that the mean perfusion EI ratio for the single patient undergoing lower lung LVRS was 0.35, consistent with lower lobe distribution of emphysema seen on CT.

Mean perfusion EI ratios for the 30 patients undergoing bilateral apical LVRS were not significantly different for the right and left lungs, measuring 3.4±2.1 for all right lungs, and 3.3±2.2 for all left lungs (Student's *t* test; $P = 0.41$).

The correlations of perfusion scintigraphy EI ratios and clinical outcome measures are given in Table 3. Perfusion EI ratios in patients undergoing biapical LVRS had a fair-to-moderate correlation with the percent change in FEV_1 measured at 3 months ($r = 0.37$, $P = 0.04(3)$, 6 months ($r = 0.36$, $P = 0.05(2)$ and 12 months ($r = 0.42$; $P = 0.034$) after surgery. Correlation with the TDI was moderate at 6 months ($r = 0.48$, $P = 0.014$). An EI ratio of greater than or equal to 3 was consistently associated with a TDI score of 5 or greater, indicating a significant improvement in dyspnea at 6 months. No correlation of perfusion ratios was seen for the 6MWT outcome measure. Figure 5 illustrates by scatterplot the relationships between the SPET EI ratio and the perfusion EI ratio, and the SPET EI and the perfusion EI, for the upper and lower halves of the lungs.

Discussion

Pulmonary emphysema is defined as “a condition of the lung characterized by abnormal, permanent enlargement of the air spaces distal to the terminal bronchioles accompanied by destruction of their walls” by the Ameri-

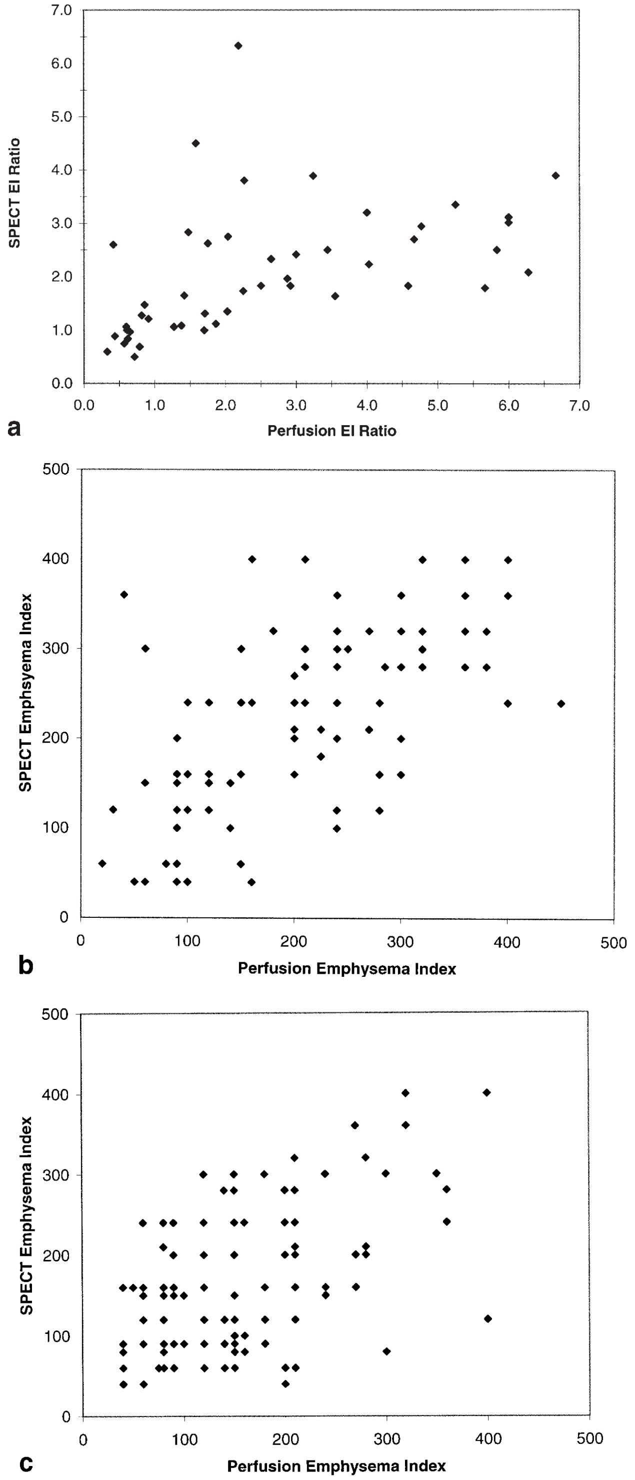

Fig. 5a–c. **a** Scatterplot of perfusion scintigraphy vs SPET EI ratios (r = 0.48). **b**,**c** Scatterplots of perfusion scintigraphy vs SPET EI for **b** upper half and **c** lower half of the lungs (r = 0.65 and 0.45 respectively)

can Thoracic Society [15]. Medical management is supportive, and emphysema is a severely progressive and often fatal condition. Lung volume reduction surgery for emphysema was first described in 1957 by Dr. Otto Brantigan in 26 patients, 53.8% of whom were able to return to work,with 23.1% obtaining symptomatic relief (n = 6) [16]. However, the procedure fell out of favor due to technical problems associated with persistent air leaks and mortality (19.2%) [17, 18]. New techniques in lung surgery [19] and improvements in both preoperative evaluation and postoperative support have resulted in a rekindling of interest in the surgical management of emphysema. Severe emphysema results in near-maximum expansion of the lungs and chest wall, with a loss of lung compliance leaving only a small tidal volume for gas exchange. The destruction of elastic tissue in emphysema reduces support to bronchi, facilitating airway collapse during expiration and air trapping [20]. During LVRS, severely diseased nonfunctional lung tissue is excised from the periphery of the lung in a series of stapling or plication maneuvers. The overall volume of the lung is reduced by 20%–30%, care being taken to produce a shape that will fill the thorax and reduce postoperative pleural air spaces. Brantigan cautioned about over enthusiastic removal of diseased lung, as the remaining lung may not be able to expand and fill the pleural space [16, 21]. The reduced total lung volume allows greater chest wall and diaphragmatic excursion, thereby increasing tidal volume. By reducing the volume of diseased lung, the radial elastic pull on the bronchi may be improved, reducing expiratory airway collapse [16, 20, 21].

LVRS is an evolving surgical procedure for the treatment of patients with severe emphysema. Given the large numbers of potentially eligible patients with severe emphysema, criteria to identify candidates for LVRS who will have a good clinical outcome are essential for optimal resource utilization. A large multicenter trial sponsored by the National Heart Lung and Blood Institute and the Health Care Financing Administration has recently been initiated to carefully evaluate the outcome after LVRS versus maximal medical therapy (including pulmonary rehabilitation) and selection criteria for LVRS in a prospective manner.

LVRS is performed at our institution for patients with severe emphysema refractory to medical management. Typically, patients selected for the procedure have upper lobe predominant emphysema on CT and chest radiographs approached surgically via median sternotomy. Generally, diffuse disease is considered less appropriate for reduction surgery, with greater improvement in lung function following bilateral apical stapling [22–24]. Patients with basal predominant disease are also amenable to surgery by bilateral thoracotomy or thoracoscopy. Patients undergoing surgery at our institution typically have an FEV_1 of between 15% and 35% of predicted, without severe CO_2 retention (PCO_2<55 mmHg). Patients undergo dobutamine echocardiography and when appropriate, right heart catheterization to evaluate for pulmonary arterial hypertension and right ventricular hypertrophy, relative contraindications to surgery. All patients also complete a 6-week pulmonary rehabilitation program with the goal of walking at 1 mph for 30 min on a treadmill.

Lung perfusion scintigraphy provides both a qualitative and a quantitative assessment of differential pulmonary parenchymal perfusion, locating areas of maximal reduction in blood flow [25], and therefore the most nonfunctioning emphysematous lung amenable to resection. V/Q scintigraphic imaging with SPET provides anatomical location of areas of decreased perfusion in the lungs. Computer-generated SPET images provide three-dimensional and cross-sectional display of the perfusion abnormalities, providing physiologic information not provided by other cross-sectional imaging, such as CT. However, the EI index for planar perfusion scans and SPET images correlated moderately with each other as demonstrated by scatterplots (Fig. 5), suggesting that there is little added benefit from the additional time and cost of adding SPET to the scintigraphic evaluation when inspected visually and scored semi quantitatively. While visually appealing, qualitative SPET did not appear to add unique information beyond that available from careful analysis of planar perfusion scintigraphy. These results corroborate those of others (Graham MM et al., presented at the American Thoracic Society meeting, May 1997). Quantitative SPET with attenuation correction has not been applied to this type of evaluation, and could prove more useful than semi-quantitative scoring of SPET data.

Patients having LVRS have more severe and extensive apical perfusion deficits than patients excluded from LVRS for diffuse disease, with a mean perfusion EI ratio of 3.3 for the 30 patients undergoing bilateral apical LVRS and 1.2 for the 17 patients excluded for diffuse disease. These findings are consistent with the anatomic basis of disease for which patients were screened for surgery during our evaluation process. In addition, the clinical outcomes measured after LVRS demonstrated moderate-to-good correlation at 3, 6 and 12 months with the perfusion EI ratios, specifically the percent change in FEV_1 at all three time points, and with the TDI at 6 months. Patients with higher ratios, and therefore relatively more severe perfusion abnormalities and more severe emphysema in the upper lungs compared with the lower lungs, had the greatest clinical improvements after surgery. This confirms the work published by Wang et al., which demonstrated that upper lobe predominance of emphysema, as indicated by more severe perfusion abnormalities in the upper lobes, was a predictor of the increase in FEV_1 6 months after biapical LVRS [26]. All of our patients with EI ratios of greater than or equal to 3 demonstrated moderate to high TDI scores at 6 months after biapical LVRS (i.e. patients undergoing LVRS with the most severe and localized upper lobe perfusion defects had the greatest functional improvement).

While scintigraphic preoperative anatomic/physiologic evaluation by perfusion scintigraphy provides useful preoperative information, ventilation scintigraphy using ^{99m}Tc-DTPA aerosol was not found to be useful owing to the high frequency of central airway tracer deposition. It is not surprising that turbulent airflow with variable central deposition of radiotracer occurred in nearly half of our patients with severe emphysema. Based on this analysis, we no longer include aerosol ventilation studies in our scintigraphic work up of LVRS candidates. In xenon gas ventilation studies, central deposition is ot a feature [20], and ultra fine aerosols such as Pertechnegas may also be promising in the future [27, 28].

Perfusion scintigraphy provides a good map of physiologic functioning lung tissue when compared to CT scans, which display the alterations in anatomy seen in obstructive lung disease. These two studies may provide complementary, but not exclusive information. For instance, one patient in this series who underwent biapical LVRS had bibasilar scintigraphic perfusion defects with an EI ratio of 0.5. The CT scan demonstrated anatomically diffuse emphysema, with a CT ratio of percent emphsyema in the upper lungs versus the percent emphysema in the lower lungs of 1.0, calculated from helical CT data using an attenuation threshold of –900 Hounsfield units and less to represent emphysema [29]. The reason for this discrepancy is unclear; no pulmonary embolus work-up was undertaken. Also, three patients denied surgery for diffuse emphysema on CT had biapical scintigraphic perfusion defects; one of these three patients also had bibasilar perfusion defects, while the other two scintigraphically had an appearance suitable for biapical LVRS. These unexpected findings emphasize the need for multimodality and functional assessment of pulmonary disease prior to surgery.

Semi-quantitative perfusion scintigraphic data may help select patients for surgery, and function as a predictor of clinical outcome after surgery. Quantitative analysis of scintigraphic data may improve the performance of this technique. Comparison of scintigraphy to both semi quantitative and quantitative chest CT as outcome predictors after LVRS will be of interest in the future.

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