Correlation of ^{68}Ga Ventilation–Perfusion PET/CT with Pulmonary Function Test Indices for Assessing Lung Function

Pierre-Yves Le Roux[1,2], Shankar Siva[1,3], Daniel P. Steinfort[3,4], Jason Callahan[1], Peter Eu[1], Lou B. Irving[3,4], Rodney J. Hicks[1,3], and Michael S. Hofman[1,3]

[1]Division of Radiation Oncology and Cancer Imaging, Peter MacCallum Cancer Centre, East Melbourne, Australia; [2]Department of Nuclear Medicine, Brest University Hospital, EA3878 (GETBO) IFR 148, Brest, France; [3]The University of Melbourne, Parkville, Australia; and [4]Respiratory Medicine, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Australia

Pulmonary function tests (PFTs) are routinely used to assess lung function, but they do not provide information about regional pulmonary dysfunction. We aimed to assess correlation of quantitative ventilation–perfusion (V/Q) PET/CT with PFT indices. **Methods:** Thirty patients underwent V/Q PET/CT and PFT. Respiration-gated images were acquired after inhalation of ^{68}Ga-carbon nanoparticles and administration of ^{68}Ga-macroaggregated albumin. Functional volumes were calculated by dividing the volume of normal ventilated and perfused (%NVQ), unmatched and matched defects by the total lung volume. These functional volumes were correlated with forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), FEV1/FVC, and diffusing capacity for carbon monoxide (DLCO). **Results:** All functional volumes were significantly different in patients with chronic obstructive pulmonary disease ($P < 0.05$). FEV1/FVC and %NVQ had the highest correlation ($r = 0.82$). FEV1 was also best correlated with %NVQ ($r = 0.64$). DLCO was best correlated with the volume of unmatched defects ($r = -0.55$). Considering %NVQ only, a cutoff value of 90% correctly categorized 28 of 30 patients with or without significant pulmonary function impairment. **Conclusion:** Our study demonstrates strong correlations between V/Q PET/CT functional volumes and PFT parameters. Because V/Q PET/CT is able to assess regional lung function, these data support the feasibility of its use in radiation therapy and preoperative planning and assessing pulmonary dysfunction in a variety of respiratory diseases.

Key Words: PET/CT; ventilation; perfusion; pulmonary function tests; chronic obstructive pulmonary disease

Pulmonary function tests (PFTs) are simple, noninvasive, and well-established physiologic investigations that provide reliable information about global lung function (*1*). However, they may be insensitive for detection of early pulmonary dysfunction (*2,3*) and do not provide spatial information about regional pulmonary dysfunction (*4*). Although PFTs measure the mechanics of gas exchange properties of the lungs, they provide limited information about pulmonary blood flow, a key component of gas exchange in the lung. Establishing a functional map of the regional ventilation and perfusion in the lungs is highly relevant to understanding the physiologic features of the lungs in many clinical situations, including individualizing and adapting radiation therapy planning (*5,6*), predicting postoperative lung function after lung resection in lung cancer patients (*7*), or predicting clinical outcomes after lung volume reduction surgery in patients with emphysema (*8*).

The principle underlying ventilation–perfusion (V/Q) scintigraphy is attractive for lung function assessment because it simultaneously assesses and compares the regional distribution of the 2 major determinants of gas exchange in the lungs. Ventilation is imaged after inhalation of inert gases or radiolabeled aerosols, such as ^{99m}Tc-labeled aerosol (Technegas; Cyclopharm), that reach terminal bronchioles in proportion to regional distribution of ventilation (*9*). Perfusion is imaged after intravenous administration of ^{99m}Tc-labeled macroaggregated albumin particles, which are trapped in the lung capillaries so that local concentration is related to the regional pulmonary blood flow. However, the relatively low spatial and temporal resolution of conventional V/Q scintigraphy has limited accurate mapping and quantification of ventilation and perfusion functional volumes and of their relationship throughout the lung (*10,11*).

Our group has demonstrated the feasibility of transitioning from conventional single-photon techniques to PET technology for V/Q imaging (*12*). ^{99m}Tc can be substituted by ^{68}Ga, a positron-emitting radionuclide, to label the same carrier molecules as conventional V/Q imaging. Ventilation imaging can be performed with ^{68}Ga-carbon nanoparticles using the same synthesis device as Technegas, yielding Galligas (*13*). Perfusion imaging can be performed with ^{68}Ga-macroaggregated albumin. As with other areas of nuclear medicine, PET offers a unique opportunity to dramatically improve the diagnostic performances of V/Q imaging because of its higher sensitivity, spatial resolution, speed of acquisition, and quantitative capability in comparison to conventional V/Q scanning (*14–17*).

Because of these characteristics, high-resolution quantitative V/Q PET/CT imaging may provide new insights for lung function assessment. The aim of the study was to correlate key pulmonary function test indices with global lung functional volumes computed with V/Q PET/CT.
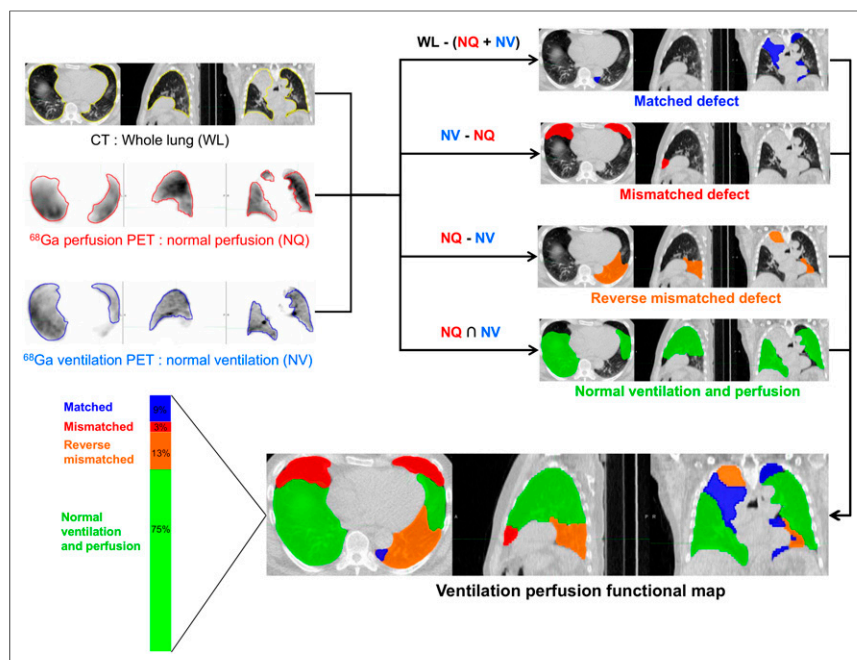
FIGURE 1. Lung functional volume calculation. WL volume, areas with normal perfusion (NQ), and areas with normal ventilation (NV) were delineated on CT, perfusion PET, and ventilation PET images, respectively. Lungs were then mapped according to relationship between ventilation and perfusion distribution in 4 physiologic conditions: matched defects, reverse mismatched defects, mismatched defects, or normal ventilation and perfusion (NVQ). Functional volumes were expressed as percentage of WL.

MATERIALS AND METHODS

Patients

Thirty consecutive patients (19 men, 11 women; mean age, 65 y; age range, 46–89 y) were prospectively recruited. All had locally advanced or inoperable non–small cell lung cancer and were scheduled to undergo radiation therapy with curative intent as part of a prospective study (Australian-New-Zealand Clinical Trial Registry Trial ID 12613000061730). All patients underwent PFTs and V/Q PET/CT as part of pretreatment evaluation. Fifteen of these 30 patients were previously included in a study that investigated the effects of respiratory motion on V/Q scanning (18). The study was approved by the institutional ethics committee, and all patients provided written informed consent.

PFTs

Spirometry was quality controlled according to the guidelines of the European Respiratory Society and American Thoracic Society (19). Forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and diffusing capacity for carbon monoxide, corrected for the patient's hemoglobin (DLCO), were measured according to the guidelines (20). Results were expressed as an absolute value (FEV1/FVC) and a percentage of predicted.

Patients were categorized according to the presence and grade of chronic obstructive pulmonary disease (COPD) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (1). DLCO was also dichotomized according to the presence of severe impairment defined as DLCO less than 55% predicted (21).

V/Q PET/CT Protocol

All patients underwent a respiration-gated V/Q PET/CT scan acquired on a Discovery 690 PET/CT scanner (GE Healthcare) using a procedure that we have previously described (18). Ventilation images were acquired after inhalation of Galligas prepared using a Technegas

generator (Cyclopharm). Perfusion images were acquired after intravenous administration of ^{68}Ga-macroaggregated albumin.

Volumetric Assessment of Ventilation and Perfusion Function with V/Q PET/CT

The lung functional volumes were contoured using MIMimage analysis software (MIM 5.4.4; MIMSoftware).

Whole-Lung (WL) Volume Delineation. The phase of the respiratory cycle during which the PET and CT images were best aligned was chosen for delineation. This was generally in the mid-time expiratory phase of the breathing cycle. The WL was then delineated on the chosen CT scan. An automatic contouring of the lungs based on Hounsfield unit value was initially performed and then visually adjusted to match normal contours if required.

Ventilation and Perfusion Volume Delineation. PET images were independently reviewed to delineate pulmonary regions with normal ventilation and normal perfusion. Areas of normal ventilation and perfusion were defined by a nuclear medicine physician experienced in interpreting V/Q imaging.

Combined Ventilation and Perfusion Lung Volume Calculation. The percentage of lung volume with normal and abnormal function was computed for several parameters including normal ventilation and perfusion, normal perfusion but abnormal ventilation (reverse mismatched), normal ventilation but abnormal perfusion (mismatched), and abnormal ventilation and perfusion (matched). Accordingly, the sum of these 4 was equal to 100%. The percentage of lung volume with normal perfusion but abnormal ventilation or normal ventilation but abnormal perfusion (unmatched) was also computed. Figure 1 illustrates the methodology used to compute lung functional volumes.

Statistical Analysis

All statistical tests were performed using GraphPad Prism 5 (GraphPad Software). The Spearman rank correlation test was used to calculate correlations between V/Q PET/CT functional volumes and PFT indices. The 2-tailed Mann–Whitney U and Kruskall–Wallis tests were used for comparison of differences between groups. The null hypothesis was rejected when P was less than 0.05.

RESULTS

The mean FEV1/FVC was 64% (range, 34%–88%), and the mean FEV1 was 61% predicted (range, 32%–126%). Eighteen patients (60%) had COPD (FEV1/FVC < 70), with 7 GOLD stage I, 8 GOLD stage II, and 3 GOLD stage III. Mean FVC was 80% (range, 58%–134%). DLCO was available in 29 of 30 patients. Mean DLCO was 63% predicted (range, 27%–102%). DLCO was lower than 55% in 10 patients.

Comparison of V/Q PET/CT Functional Volumes with PFT Indices

Figure 2 shows an example of a V/Q lung functional map and quantification with V/Q PET/CT. Correlations of V/Q PET/CT functional volumes and PFT parameters are shown in Table 1.
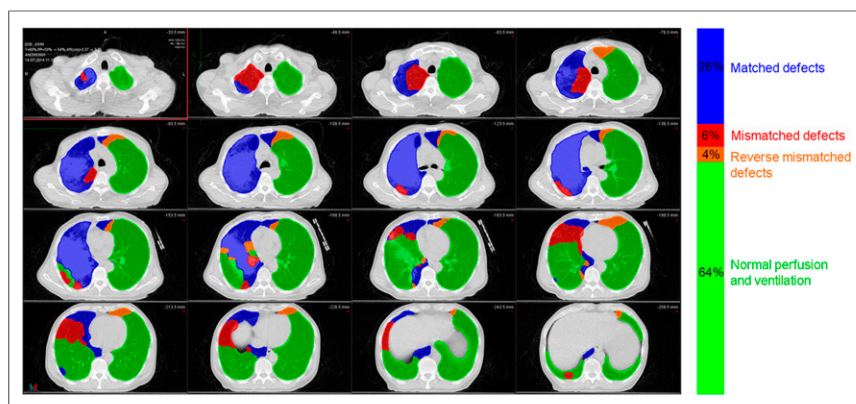
FIGURE 2. Example of lung functional map and quantification with V/Q PET/CT.

FEV1/FVC. The percentage of lung volume with normal perfusion and ventilation (%NVQ) correlated most strongly with FEV1/FVC ($r = 0.82$) (Fig. 3A). Correlation was also high with the percentage of lung volume with normal perfusion, normal ventilation, and matched defects (r range, 0.78–0.81). All V/Q PET/CT functional volumes were significantly different in patients with COPD, compared with patients without COPD ($P < 0.05$) (Fig. 4A).

FEV1. %NVQ also demonstrated the highest correlation with FEV1 ($r = 0.64$) (Fig. 3B). Figure 4B shows a V/Q PET/CT functional profile in relation with the degree of obstruction according to GOLD. There was a significant difference according to the grade of the degree of obstructive syndrome (i.e., FEV1 > 80, 50–80, or < 50) with the percentage of lung volumes with normal perfusion, normal ventilation, normal ventilation and perfusion, and matched defects ($P < 0.05$).

DLCO. The percentage of lung with unmatched defects (i.e., either mismatched or reverse mismatched defects) demonstrated highest correlation with DLCO ($r = 0.55$) (Fig. 3C). All V/Q PET/CT functional volumes were significantly different in patients with severe impairment of DLCO (DLCO < 55% predicted) ($P < 0.05$) (Fig. 4C).

FVC. No correlation was found between FVC and V/Q PET/CT functional volumes.

Comparison of V/Q PET/CT Functional Volumes with Global Lung Function Impairment

When %NVQ only was considered, a cutoff value of 90% correctly categorized 28 of 30 patients (93%) with or without significant pulmonary function impairment (defined by confirmed COPD or severe impairment of DLCO) (Fig. 5). Eight patients had more than 90% of lung volume with normal ventilation and perfusion, and all were free from significant pulmonary disease. Of the 22 patients demonstrating less than 90% of lung volume with normal ventilation and perfusion, 20 (91%) had COPD or DLCO less than 55% predicted.

DISCUSSION

In the present study, we aimed to validate the regional functional information obtained from this new imaging tool with routine global pulmonary functional assessments. The regional matching of ventilation and perfusion is a key physiologic principle governing efficient gas exchange by the lungs. Accordingly, V/Q PET/CT technology allows mapping of the relationship between ventilation and perfusion distribution throughout the lung, identifying 4 physiologic patterns: areas with functional ventilation and perfusion, reversed mismatched defect, mismatched defects, and matched defects, respectively. Results were expressed as percentage of WLs. Thus, V/Q PET/CT provides simple, easily understandable, and physiologically meaningful information about lung function.

We showed a high degree of correlation between functional lungs volumes on V/Q PET/CT and lung function as assessed by PFTs. The strongest correlation was achieved between FEV1/FVC and the percentage of lung volume with normal ventilation and perfusion (%NVQ). The high correlation between global measures of lung ventilation and perfusion concordance with PFT supports the validity of using regional measures of lung function derived using this technique in predicting the consequences of therapies that affect regional function, such as surgery or radiotherapy. DLCO was best negatively correlated with the percentage of lung volume with unmatched defects, underpinning the importance of matched ventilation and perfusion to gas exchange. Overall, %NVQ higher than 90% correctly identified significant lung function impairment (defined by COPD or DLCO < 55%) in 93% of patients.

In the past decades, V/Q imaging has been an evolving technology with the introduction of SPECT imaging, the development of hybrid SPECT/CT devices, and the use of new radiotracers for ventilation (22). Advances have improved the

TABLE 1
Spearman Correlation Results Between V/Q PET/CT Functional Volumes and PFT Parameters

V/Q PET/CT functional volumes	% normal perfusion	% normal ventilation	% normal ventilation and perfusion	% reverse mismatch	% mismatch	% unmatch	% match
FEV1/FVC	0.81*	0.78*	0.82*	−0.58*	−0.62*	−0.70*	−0.79*
FEV1	0.62*	0.61*	0.64*	−0.45*	−0.55*	−0.59*	−0.62*
DLCO	0.47*	0.43*	0.48*	−0.45*	−0.51*	-0.55*	−0.42*
FVC	0.28	0.30	0.31	−0.21	−0.21	−0.24	−0.31

*$P < 0.05$.
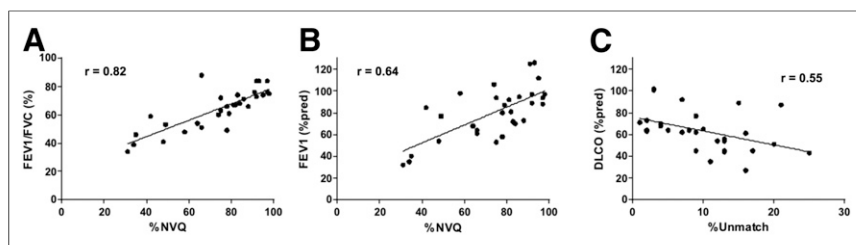
FIGURE 3. Relation between FEV1/FVC and percentage of lung volume with normal ventilation and perfusion (%NVQ) (A), FEV1 and %NVQ (B), and DLCO and percentage of lung volume with unmatched defects (%Unmatch) (C). Inserted lines represent regression line.

diagnostic performances of the test especially in pulmonary embolism diagnosis (23,24) and also in lung functional assessment (25,26). However, the relatively low resolution of SPECT imaging makes accurate delineation and quantification of lung functional volumes difficult (11). The introduction of PET imaging has dramatically increased the possibilities of nuclear medicine imaging. The principles of SPECT and PET—both molecular imaging techniques that can evaluate physiologic, biologic, and biochemical processes—are similar, but current PET technology has clear technical superiority compared with SPECT, with higher sensitivity for detecting radioactive decay, higher resolution, and superior quantitative capability (14–16).

Most patients studied in this cohort had COPD of varying severity. All V/Q PET/CT functional volumes were different in patients with COPD. The change of all functional volumes highlights the heterogeneity and complexity of the pathophysiology underlying COPD, which affects proximal and peripheral airways, lung parenchyma, and pulmonary vasculature (27,28). Pathologic changes include structural changes resulting from repeated injury and repair in different parts of the lung and chronic inflammation (4). Among all V/Q PET/CT functional volumes, the most relevant parameter in predicting the degree of obstruction was the %NVQ, with strong correlation with FEV1/FVC ($r = 0.82$) and FEV1 ($r =$

0.64). This strong correlation indicates that physiologic impairment due to matched or unmatched defects is associated with the pathologic changes related to COPD and is involved in the pathophysiology of the obstructive syndrome as described by PFTs.

The correlation was weaker but still significant with DLCO. DLCO is an indicator of abnormal gas exchange, whose determinants are complex, involving both the function of alveolar membrane and the pulmonary blood pool. The strongest correlation was with the percentage of lung volume with unmatched defects rather than with matched defects or normal function. For patients with DLCO greater than or less than 55, the mean percentage of unmatched volume was 7% and 15%, respectively ($P < 0.05$). In this study, V/Q inhomogeneity was therefore an essential determinant of DLCO impairment.

Although PFTs enable the assessment of global lung function, a key advantage of V/Q imaging is to assess regional lung function. In particular, V/Q PET/CT provides 4 physiologic patterns that give information that could be physiologically and clinically important. There are many pulmonary conditions in which accurate imaging of regional changes in the lungs would be of high interest. These conditions include radiotherapy planning to minimize dose to functional lung in order to decrease the risk of radiation pneumonitis (5,29), presurgical evaluation of patients undergoing bronchoscopic or surgical lung volume reduction surgery (8,30), and assessment of pulmonary reserve before pulmonary resection surgery (7). Several imaging techniques have been proposed to provide a regional assessment of lung function (31,32), but none of them has positioned itself as a reference modality and has been translated to routine clinical use. In patients with pulmonary disease, V/Q PET/CT seems to be capable of identifying focal areas responsible for lung function impairment. Additional prospective studies are needed to assess the relevance of a personalized approach based on V/Q PET/CT in the management of patients with pulmonary disease.

One of the limitations of the study is that we compared functional volumes on V/Q PET/CT with various PFT indices, which do not measure or express the same physiologic process. As an example, FEV1/FVC, which represents the volume of air expired in the first second expressed as a percentage of FVC, was compared with the percentage of the WL volume with normal perfusion and ventilation. In addition, PFTs are routinely interpreted as a multiparametric examination, and isolated values such as FEV1 or DLCO, although directly impaired by local therapies, have only limited significance (33,34). Nevertheless, a cutoff value of 90% for %NVQ correctly classified 100% of patients without pulmonary function impairment and 91% of patients with significant pulmonary function impairment, whatever the underlying pathology (COPD or severe DLCO impairment). High-resolution imaging of functional volumes with V/Q
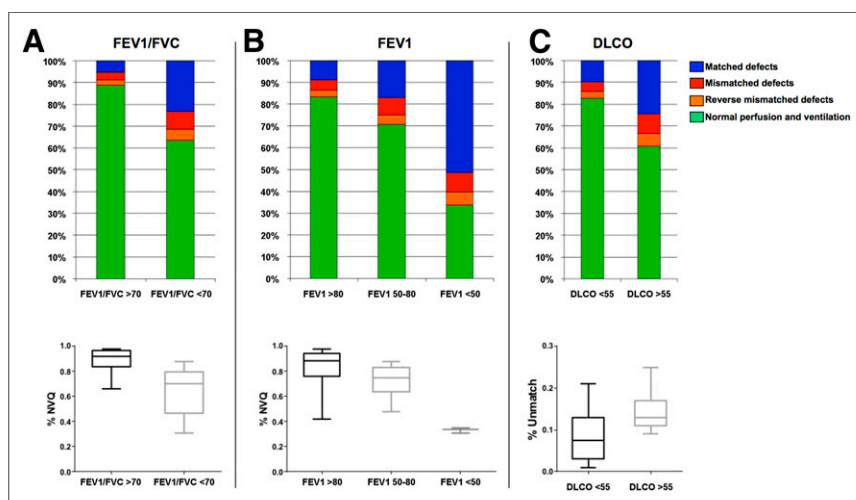
FIGURE 4. V/Q PET/CT functional profile in relation with FEV1/FVC (A), FEV1 (B), and DLCO (C). Upper graphs shows mean functional volumes according to pulmonary function test parameter. Lower graphs show minimal, maximal, median, 25% and 75% quartiles for most discriminant functional volume, that is, percentage of WL with normal ventilation and perfusion (%NVQ) for FEV1/FVC and FEV1, and percentage of WL with unmatched defects (%Unmatch), that is, either mismatched or reverse mismatched defects.

FIGURE 5. V/Q PET/CT functional profile in patients with COPD and DLCO impairment. V/Q PET/CT functional volumes (percentage of lung volume with normal ventilation and perfusion, reverse mismatched, mismatched, and matched defects) of 30 patients. Below is mentioned presence and grade of COPD and presence of severe DLCO impairment. Cutoff value of 90% normal ventilation and perfusion correctly identified significant pulmonary disease in 28 of 30 patients (93%).

PET/CT may provide not only a pulmonary functional map, but also a new quantitative tool to assess lung dysfunction. Another limitation of the study is that the visual contouring method used is time consuming, possibly limiting its use in clinical practice. Further research would be of value to assess automated or semiautomated contouring methods that would provide reproducible and quick methodology.

Besides these promising findings in relation to regional and global lung function assessment, V/Q PET/CT technology offers many additional advantages. It is a noninvasive modality that does not rely on patient effort, except the need to breathe the radioactive gas for a few seconds and to lie relatively still on the PET/CT camera bed during the acquisition time. The acquisition time is low, about 15–20 min with our protocol, and could probably be reduced because of the high sensitivity of PET technology. As with V/Q scintigraphy, there are no known contraindications or acute side effects (allergy) associated with the radiotracers. The effective radiation dose of the scan is low, approximately 2 mSv for the PET acquisition plus an additional 1–2 mSv for the low-dose CT component, equivalent to the dose of V/Q SPECT/CT. Finally, ^{68}Ga is produced by an on-site generator enabling on-demand availability similar to ^{99m}Tc but with a longer shelf-life of 9–12 mo versus 1–2 wk for the ^{99m}Tc generator. The ^{68}Ga generator is increasingly available because of its use for neuroendocrine (35) and prostate cancer imaging. With PET/CT and ^{68}Ga becoming increasingly available, we envisage that widespread adoption of V/Q PET/CT could become a reality.

CONCLUSION

V/Q PET/CT is an imaging tool that allows high-resolution measurement of ventilation and perfusion distribution in the lungs. It allows regional quantification of the relationship between the 2 key components of gas exchanges in the lungs. In the present study, we showed a high degree of correlation between V/Q PET/CT functional lung volumes and PFT parameters, suggesting significant potential in the management of patients with pulmonary disease, especially where understanding of regional lung function is likely to influence clinical decision making. Further research is required in larger cohorts to compare the prognostic utility of functional lung volumes undertaken with V/Q PET/CT and PFTs in a range of pulmonary disease.

DISCLOSURE

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